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THE TREATMENT OF HAY FEVER AND ASTHMA WITH VIOSTEROL OF HIGH POTENCY* †

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AN ACCOUNT was given in an earlier publication[1] of the treatment of six cases of hay fever and asthma with viosterol of high potency during the season of 1932. This experience was sufficiently encouraging to justify further investigation. During the season of 1933, including these same six subjects, a group of 250 subjects was enrolled. But the statistical treatment in this paper includes only 212 subjects. After careful study of the case histories some were eliminated, either because the histories were not sufficiently complete or because it became apparent that certain subjects were not pure allergic cases, or because there was lack of intelligent cooperation. Still others had withdrawn for various reasons.

Of the 212 subjects there were 114 male and 96 female patients, ranging in age from five to sixty-five years. The detailed case histories and the results of extensive chemical investigations will be presented in a later publication. It is the purpose of this paper to give as a preliminary report a condensed summary and the conclusions to be drawn.

All the subjects treated in 1932 were available during the second season. Of the total group, 68 received only viosterol during the season of 1933 (Tables I and II). Another group of 69 subjects, none of whom had been treated by any means in 1932, received both viosterol and pollen injections (Table III). A third group of 75 subjects, all of whom

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had been treated by pollen injections during 1932 by one of the authors, were, during 1933, given viosterol in addition to the pollen injections. In Table IV are shown the results in this group, also a comparison with the results obtained in 1932 in these same patients when the pollen treatment alone was used.

TABLE I

NUMBER AND DISTRIBUTION OF SUBJECTS RECEIVING ONLY VIOSTEROL TREATMENT DURING THE SEASON OF 1933

	NO RELIEF	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTALS
INDEX OF RELIEF	0	2.5	5	7.5	9	10	
	0	3	5	9	4	1	22
Hay fever		4.4%	7.3%	13.2%	5.9%	1.4%	32.3%
	5	4	23	8	4	2	46
Asthma	7.3%	5.9%	33.8%	11.7%	5.9%	2.9%	67.6%
	5	7	28	17	8	3	68
Total	7.3%	10.3%	41.2%	24.9%	11.7%	4.4%	

TABLE II

THE RELATION OF VIOSTEROL DOSAGE TO DEGREE OF RELIEF

	NO RELIEF	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTALS
INDEX OF RELIEF	0	2.5	5	7.5	9	10	
Drops viosterol daily							
20	1	1			2		4
30			3				3
40				1		1	2
45	1						1
50	1						1
60			1				1
	3	1	4	1	2	1	12

One of the difficulties encountered in this work was the accurate evaluation of the degree of relief experienced by each patient. In order to obtain as much exact data as possible each was given a form to be filled out daily with a record of the number and severity of attacks of sneezing, the presence or absence of other nasal symptoms, of ocular symptoms or of asthma, the number of hours of sleep during the night, and, finally, the general impression of the patient as to whether the symptoms had been mild, moderate or severe that day.

In the absence of any symptoms or in the presence of mild symptoms with no signs of increasing severity, a patient was interviewed and examined only once a week. If symptoms were more than mild or of increasing severity, the patient was thoroughly examined at least twice a week, sometimes more frequently.

It was found later that the frequency of examination was an important factor in classifying the subject as to the degree of relief. One of the most helpful questions for those who were not completely but very

TABLE III

COMBINED VIOSTEROL AND POLLEN TREATMENT IN 1933, NO TREATMENT IN 1932

	0	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTAL
Hay fever	2		2	10	10	7	31
	(2.9)		(2.9)	(14.5)	(14.5)	(10)	(44.9)
Asthma	1		5	9	14	9	38
	(1.45)		(7.24)	(13)	(20.3)	(13)	(55)
Total	3		7	19	24	16	69
	(4.3)		(10)	(27.5)	(36.2)	(23.3)	

Figures in parentheses are percentages of the total.

TABLE IV

SUBJECTS TREATED WITH POLLEN ONLY IN 1932, COMBINED POLLEN AND VIOSTEROL IN 1933

	NO RELIEF	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTALS
INDEX OF RELIEF	0	2.5	5	7.5	9	10	
	15	8	17	20	14	1*	75
1932	20%	10.7%	22.6%	26.6%	18.6%	1.3%	
	1	1	13	22	22	16	75
1933	1.3%	1.3%	17.3%	29.3%	29.3%	21.3%	

*This case was included by error as explained in the text.

greatly relieved, was whether the individual would have considered it at all necessary to resort to medication for relief from the symptoms actually present.

In addition to the daily record kept by each patient and the frequent interviews and examinations by one of the authors, a list of specific questions was given to each patient at the end of the season. This furnished additional data for comparing the condition during the season in question with previous seasons.

There is no generally accepted method for recording the results of therapy since the symptoms of hay fever or asthma are not readily re-

duced to quantitative measurement. Not only does the classification vary with different authors, but the factor of the personal element involved in evaluating the results and classifying treated patients makes a comparison of results obtained by different workers of questionable value. This difficulty was avoided in this work by including in the group receiving the combined viosterol and pollen treatment in 1933 as many subjects as possible who had received pollen treatment only by one of us (B. Z. R.) in 1932.

Thus, the results were compiled by the same person from data supplied by the same subjects. It is believed, therefore, that the conclusions to be drawn from a comparison of the results in the two seasons on this basis are valid. The fact that the pollen count in the Chicago area was 20 per cent higher in 1933 than in 1932, was not involved in the statistical comparison. If this could be taken into account, it would make the record for the 1933 season even more favorable.

Taking all facts into consideration it was finally possible to arrive at an approximate evaluation of the clinical results in each subject. The classification used was as follows: "complete relief" with no symptoms of hay fever or asthma present throughout the season; "almost complete" when symptoms were so mild and inconstant that the subject did not find it necessary to resort to medication for relief; "satisfactory" when the symptoms were not severe enough to handicap the subject in the usual activities or occupation; "moderate" when, on the basis of the number of days involved or the number of daily attacks or the extent of modification of activity, it could be concluded that the patient had experienced at least 50 per cent relief; "slight" relief when the degree was less than moderate; a sixth group comprised those that were not relieved in any way by the treatment.

In order to assist further in the evaluation, an index of relief was assigned to each group in the classification: "complete" relief, 10; "nearly complete," 9; "satisfactory," 7.5; "moderate," 5; "slight," 2.5; "no relief," 0. It will be noted that these indices do not represent an even distribution of mathematical values over the entire range, but that the three higher degrees cover a range of only 25 per cent while the remaining degrees cover 75 per cent. This fact must be taken into account in evaluating the tables.

TREATMENT WITH VIOSTEROL ONLY

Sixty-eight patients (Table I) sensitive to the ragweed pollens made up the group treated with viosterol only.

Since it was most convenient to administer viosterol in drops, the dose is so designated. Since 1 c.c. of viosterol 10,000X contains 920,000 International Units of vitamin D and since 1 c.c. is equivalent to 30 ± 2 drops,* one drop would thus contain approximately 30,000 I. U. Treat-

*This concentrated solution of viosterol forms larger drops than the dilute solution used for the treatment of rickets.

ment with viosterol was usually begun from two to four weeks before the date upon which the particular subject was accustomed to experience the first allergic symptoms. In some cases, however, as in the group in Table II, and a few others who did not report early, the preseasonal treatment was much shorter. In general, it appears that a preseasonal period of ten days is probably quite as effective as a longer period, although we cannot be absolutely certain of this at present.

The initial dosage ranged from 4 to 10 drops daily and was increased as found necessary or as the individual tolerance permitted. The toxicity which sometimes occurred is discussed in another paper.[2]

Twenty-two patients of this group had uncomplicated hay fever, while 46 had both seasonal asthma and hay fever. As shown in this table, all of the 22 who had hay fever were relieved to some degree. Fourteen, or 70 per cent, of them were in the group of "satisfactory" to "complete"; that is, not less than 75 per cent relief. Of the asthma patients 41 of the 46, or 89.2 per cent, had some degree of relief. Fourteen of the number, or 30.4 per cent, were in the groups of "satisfactory" to "complete"; that is, relieved not less than 75 per cent. While the number is not large enough to make the statistics more than indicative, neither the patients nor the examiner doubted that definite benefit was derived from viosterol alone, and there was no question that in those patients classified in the groups of "satisfactory" or above the relief was marked. Even in the group designated as "slight relief" the clinical records showed that the relief was definite. The correlation of the response with the therapy was especially shown by those patients who did not start taking viosterol until well-defined hay fever or asthma had appeared, as discussed below. The rapidity of the clinical response to viosterol varied from two days to a week in those showing improvement. The difference in responsiveness does not seem to be related to the severity of the symptoms but is rather a question of individual susceptibility to viosterol therapy.

For the sake of further controlling our observations a group of 30 subjects selected at random from the general series was given a placebo of corn oil. (The viosterol consists of irradiated or activated ergosterol dissolved in corn oil.) Instructions were given in the same specific manner as to those receiving viosterol. Also, the containers in which the material was dispensed were identical with those for viosterol. Eighteen of the 30 dropped out before August 20 because they were obtaining no alleviation of symptoms. This is in contrast to the fact that 90 per cent of the treated patients of similar character continued through the season. The other 12, while equally sure that they had experienced no relief, were willing to remain longer in the hope that they might be relieved.

In general these 12 were all much more severe cases than those who

dropped out. In fact, this accounts for their willingness to continue; they were subject to such severe symptoms that they felt it more necessary to try to attain relief.

While these 12 are included in Tables I and V, it was deemed important to construct a separate table in order to show their progress after the corn oil was replaced with viosterol. (Table II.) Since none of them received viosterol until symptoms of hay fever or asthma were well advanced, it may be fairly assumed that the proportionate degree of relief was not so great as in comparable cases that had begun treatment before the onset of the season. Consequently, in Tables I and V

TABLE V

CORRELATION OF INDICES WITH DOSAGE OF VIOSTEROL

	NO RELIEF	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTALS
INDEX OF RELIEF	0	2.5	5	7.5	9	10	Totals
MAX. DOSE VIOSTEROL DAILY IN DROPS							
below 5			2 (2.9)		2 (2.9)		4 (5.9)
5-9				3 (4.4)	1 (1.4)		4 (5.9)
10-14			4 (5.9)	3 (4.4)		1 (1.4)	8 (11.7)
15-19			2 (2.9)		2 (2.9)		4 (5.9)
20-29		1 (1.4)	6 (8.8)	2 (2.9)	1 (1.4)		10 (14.7)
30-39	3 (4.4)	5	10 (14.7)	4 (5.9	1 (1.4)	1 (1.4)	23 (33.8)
40-45	2 (2.9)	1 (1.4)	3 (4.4)	4 (5.9)	1 (1.4)	1 (1.4)	13 (19)
60			1 (1.4)	1 (1.4)			2 (2.9)
Totals	5 (7.3)	7 (10.3)	28 (41.2)	17 (25)	8 (11.7)	3 (4.4)	68

the average indices of relief are reduced accordingly in all brackets to a degree that presents a less favorable showing than would probably have been the case if these 12 had been treated exactly as the others.

In Table II are shown the results with these 12 subjects after viosterol administration was actually begun. Three experienced no relief, and one only slight relief. The remaining eight, or 66 per cent, experienced definite relief, whereas in Table I, 17.6 per cent of the total of 68 viosterol-treated subjects appear in the first two brackets and 82.4 per cent in the upper four.

COMBINED THERAPY (POLLEN INJECTIONS AND VIOSTEROL)

A total of 144 ragweed sensitive patients were selected for viosterol administration in addition to the routine prophylactic pollen injections. As indicated in Table VI, 62 of these had a history of no asthma, while

82 had had pollen asthma. The results of the combined treatment are indicated in this table. As will be pointed out later, if any error in judgment was made in classifying these patients, that it was on the side of overconservatism. If any doubt existed about the classification of the degree of relief in any particular case, the lower of the two classifications involved was given preference.

Table VI indicates that 85 per cent of this group were benefited 75 per cent or more. The high percentage of "complete relief" (32 per cent) and the low percentage of "no relief" (2.74 per cent) are particularly significant in evaluating the results of this form of treatment.

TABLE VI

NUMBER AND DISTRIBUTION OF SUBJECTS RECEIVING VIOSTEROL AND POLLEN TREATMENT COMBINED DURING THE SEASON OF 1933

	NO RELIEF	SLIGHT	MODERATE	SATISFACTORY	ALMOST COMPLETE	COMPLETE	TOTALS
INDEX OF RELIEF	0	2.5	5	7.5	9	10	
Hay fever	2 1.4%	1 0.69%	8 5.5%	23 15.9%	18 12.5%	10 6.9%	62 43.5%
Asthma	2 1.4%	0	12 8.3%	18 12.5%	28 19.4%	22 15.3%	82 56.5%
Totals	4 2.8%	1 0.69%	20 13.8%	41 28.4%	46 31.9%	32 22.2%	144

TABLE VII

COMPARISON OF RESULTS IN 1932 AND 1933. COLUMN HEADS REPRESENT DEGREE OF CHANGE IN LATTER YEAR AS COMPARED TO FORMER

	LESS RELIEF	SAME DEGREE	+	++	+++	++++	
Hay fever	3	5	13	5	5		31
Asthma	6	5	10	12	6	5	44
Totals	9	10	23	17	11	5	75
Per cent	12	13.3	30.7	22.6	14.7	6.6	

An even more conclusive method for comparing the effect of prophylactic pollen injections alone and of concentrated viosterol in addition to the injections is illustrated in Tables IV and VII. Seventy-five of the patients who were included in Table V had received prophylactic pollen injections previous to the 1932 season. These were available for the combined pollen injections and viosterol treatment during the 1933 season. In selecting the group we purposely excluded all cases (except one patient who was included through error) who had had complete relief from pollen injections during the 1932 season. This was done be-

cause it seemed that we could gain nothing by additional therapy to patients who had already had complete relief through pollen injections. Table IV emphasizes the difference in the results obtained by the same patients in 1932 and in 1933. The difference is particularly noticeable when the number of patients receiving no relief in 1932—fifteen (20 per cent)—is compared with the number not relieved in 1933—one (1.33 per cent). A similar difference is noticed in the column headed "slight" relief—eight patients (22.66 per cent) in 1932, and only one patient (1.33 per cent) in 1933. In the higher divisions of the table a similar difference is found. Thirty-four patients (45.32 per cent) had from 75 per cent to 90 per cent relief in 1932, while 44 patients (58.66 per cent) received a similar degree of relief in 1933. The figures in the "complete" relief column are not directly comparable during the two years, since, as stated previously, except through the error of including one patient, those who had had complete relief during 1932 from pollen injections were not given viosterol. However, 15 patients were added to the "complete" relief column in 1933 who during 1932 had had a lesser degree of relief.

A more direct comparison is made in Table VII of the degree of relief obtained in 1933 as compared to that in 1932 by this same group of patients. The degree of relief obtained from prophylactic pollen injections during 1932 by each patient was taken as the basis for the comparison. If in 1933 the degree of relief was one division less, as from "complete" in 1932 to "almost complete" in 1933, or from "satisfactory" in 1932 to "moderate" in 1933, the patient was grouped among those relieved "slightly less." If improvement occurred during 1933 as compared to 1932, the patient was classed as +, 2+, 3+, or 4+, depending upon the difference in his condition in the two seasons. A change from "almost complete" to "complete" was thus only +, while from "slight" to "complete" classed the individual as 4+. The degree of improvement rather than the absolute amount of benefit is, therefore, indicated in this table. Of the 75 patients treated during both years, nine were slightly worse during 1933 than during 1932, ten were benefited to the same extent, while 58, or 77.33 per cent of the total, were relieved in some degree more than during 1932 as indicated in the table. The difference in the severity of the 1932 and 1933 ragweed pollen seasons, fortunately, simplifies the interpretations of these results. As previously stated, the total pollen counts in the Chicago district were 20 per cent higher in 1933 than in 1932.

It is acknowledged that the more favorable results obtained in these individuals in 1933 as compared to 1932 may be partly due to the effect of several years' consecutive treatment. The difference in results, however, is so great in the two seasons that, while this factor cannot be completely disregarded, it cannot be considered as the sole or most impor-

tant reason for the difference in the results during the two seasons. A division of the 144 patients in Table VI into those who had treatment previous to 1933 (Table IV) and those who had had no treatment previous to 1933 (Table III) indicates a close similarity of the results in the two groups. The similarity in the favorable results obtained in these two groups would indicate that the effect of previous prophylactic injections did not play an important rôle in the results reported.

What is the relationship of the pollen dosage, the viosterol dosage, the rise in the blood calcium to the degree of improvement attained by the patients? These questions can be answered by analyzing separately each

TABLE VIII

RELATION OF VIOSTEROL AND POLLEN DOSAGE TO DEGREE OF RELIEF

DROPS VIOSTEROL / MG. POLLEN N	LESS THAN 0.01	0.01–0.05	0.06–0.1	–0.2	–0.3	–0.4	TOTALS	AVERAGE INDICES OF RELIEF
Less than 5	2	22	19	14	1	1	57	
	1.45%	15.9%	13.7%	10%	0.7%	0.7%	41.3%	8.7
5-9	6	26	22	9	4	1	67	
	4.3%	18.8%	15.9%	6.5%	2.9%	0.7%	48.5%	7.54
10-14	1	3	2	3			9	
	0.7%	2.17%	1.45%	2.17%			6.5%	5.4
15-19		3	1				4	
		2.17%	0.7%				2.9%	6.9
Total	9	53	44	26	5	2	138	
	6.5%	38.4%	31.8%	18.8%	3.6%	1.45%		
Average indices of relief	6.4	7.34	8.54	8.17	7.9	7.5		

Index key—Complete relief 10
Almost complete 9
Satisfactory 7.5
Moderate 5
Slight 2.5
None 0

of these factors in relation to the degree of improvement. To do this, in Table VIII, the degree of improvement was indicated by the "index of relief," as explained previously. Each patient was given an "index number" corresponding to the degree of relief obtained. The average for each group was thus obtained. The maximum pollen dose and the maximum viosterol dose were then plotted against the average index of relief.

The relationship of the pollen dosage to the degree of improvement is indicated in Table VIII and Chart 1. The maximum pollen dose, indicated in mg. of total nitrogen, was usually attained about August 1 to 10. All except 36 of the patients treated either during 1932 or during 1933 had been treated under the supervision of one of the authors

(B. Z. R.). The 36 not under this supervision had had adequate treatment in the Allergy Clinic of the University of Illinois College of Medicine. None were included in this report who had not had at least 20 injections before August 1. To gain the maximum dose tolerated by each patient with no constitutional reactions was the aim in each case. The maximum dose, therefore, varied from 0.01 to 0.4 mg. N. The degree of improvement, however, does not maintain a constant relationship to the size of the maximum dose. There does seem to be a direct relationship between the size of the maximum pollen dose and the degree of improvement up to 0.1 mg. of nitrogen. Above that, the curve declines.

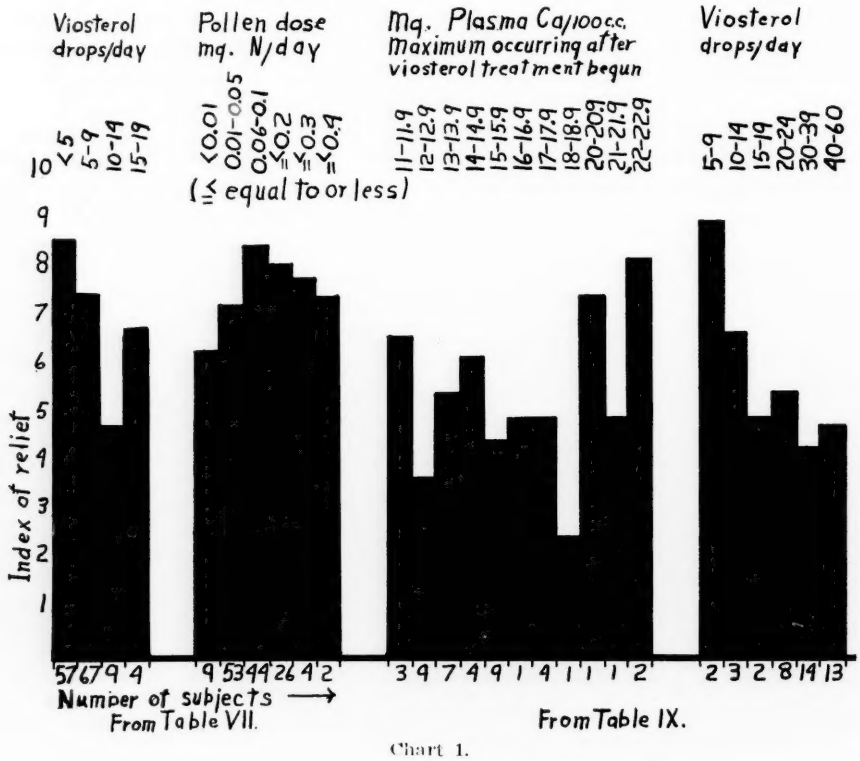

Chart 1.

Nor is there more than a maximum of 20 per cent difference between the lowest average index of relief obtained with the maximum dose of 0.01 mg. N, and the highest average index of relief obtained with the maximum dose of 0.1 mg. N. This relatively small degree of difference, together with the general appearance of the curve, seems to indicate that the differences in maximum pollen dosage bear no relationship to the degree of benefit obtained.

The relationship of the dose of viosterol that was administered to the degree of relief obtained is indicated in Tables V and VIII and Chart 1. It will be noted that the degree of improvement decreases as the viosterol

TABLE IX

MG. CA/100 C.C. PLASMA. MAXIMUM FOUND AFTER VIOSTEROL TREATMENT WAS BEGUN

CALCIUM	11-11.9	12-12.9	13-13.9	14-14.9	15-15.9	16-16.9	17-17.9	18-18.9	20-20.9	21-21.9	22-22.9	TOTALS	INDICES OF RELIEF
VIOST. DROPS													
5-9		1 (2.4)	1 (2.4)									2 (4.8)	9
10-14	1 (2.4)			1 (2.4)		1 (2.4)						3 (7.1)	6.6
15-19			2 (4.8)									2 (4.8)	5
20-24	1 (2.4)	1 (2.4)		1 (2.4)	1 (2.4)		3 (7.1)				1 (2.4)	8 (19)	5.5
30-39		5 (11.9)	4 (9.5)		4 (9.5)			1 (2.4)				14 (33.3)	4.3
40-60	1 (2.4)	2 (4.8)		2 (4.8)	4 (9.5)		1 (2.4)		1 (2.4)	1 (2.4)	1 (2.4)	13 (31)	4.8
Totals	3 (7.1)	9 (21.4)	7 (16.6)	4 (9.5)	9 (21.4)	1 (2.4)	4 (9.5)	1 (2.4)	1 (2.4)	1 (2.4)	2 (4.8)	42	5.9
Indices of relief	6.66	3.77	5.51	6.25	4.5	5	5	2.5	7.5	5	8.25	5.9	

Figures in parentheses are percentages of total.

dose increases. In considering this point it must be taken into account that most of our patients were started on small doses of viosterol between July 15 and August 1. The dose was then increased only if the patient displayed symptoms greater than mild or of increasing severity. In those not yielding readily the dose of viosterol was increased repeatedly, to a maximum of 19 drops a day in the pollen treated cases, and a maximum of 60 drops a day in those receiving viosterol only. Therefore, the less a patient improved, the more viosterol he was given up to the maximum dose indicated.

Since the original impetus to this investigation was in connection with the supposed rôle of calcium in allergy, a relationship which seems very doubtful from the results reported in the preliminary paper,[1] it seemed advisable to investigate the possible correlation of the blood calcium with the viosterol dosage and the degree of relief. In Table IX and Chart 1 are shown the results of a study of 42 of the patients treated with viosterol only.

The maximum plasma calcium concentration found after viosterol administration was begun is recorded in relation to the dose; also the average indices of relief are recorded for each group. The level of the plasma calcium varies widely in many individuals when frequent examinations are made. This was emphasized in our preliminary report.[1] In the range up to 14 mg. per 100 c.c. every subject at some time before treatment showed a calcium concentration equal to or comparable with the maximum found during or after treatment.

The number of samples drawn before treatment ranged from 4 to 15; after treatment was begun the number ranged from 5 to 16. By referring to Chart 1 it is seen that the relation between the calcium concentration and the average index of relief is entirely random; but the relation between the viosterol dosage and the average index of relief conforms to that discussed in connection with Table V.

While in every instance of excessively high blood calcium, the viosterol dose was also high, yet there were five subjects receiving from 40 to 60 drops as a maximum dose who did not at any time show a blood calcium above 14 mg. per 100 c.c.

It should be mentioned that one of the six cases treated with viosterol in 1932 was a girl seventeen years of age who had suffered from severe uncomplicated hay fever every year. She was practically completely protected in 1932. She consented to go untreated in 1933 as long as possible. One day, following a storm, she experienced rather severe hay fever which receded progressively during the next three days. At no other time during the season was there any evidence of hay fever. Thus she passed through the entire season without treatment. None of the other five were so fortunate. Whether this one case was actually rendered highly immune to pollen by the treatment or whether the mildness of her condition in 1933 was entirely independent of the previous treat-

ment cannot be determined now. If one may be permitted a speculative statement based only on the results in this one patient, the case suggests the possibility that several successive seasons of viosterol treatment in addition to pollen injections *might* finally induce a degree of alteration in sensitivity that would enable a larger proportion of patients to gain permanent immunity to pollen than is the case with the present method of treatment.

An effort will be made to follow these subjects through successive seasons to determine whether this possibility is a reality.

It is difficult to offer any explanation of our results at present. They are certainly not due to an increase in the concentration of total blood calcium or to any consistent alteration in the calcium partition in the blood. There does appear, however, to be a significant relation to the potassium-calcium ratio. The only significant consistent change in the blood chemistry was in this factor. In the control period there was considerable fluctuation in the ratio which disappeared to a large degree after treatment with viosterol was instituted. The general level of the ratio was lowered considerably. A further study of this relationship is being made.

SUMMARY

1. A study has been made of 212 patients suffering from seasonal hay fever and asthma. Of these, 68 were treated with viosterol 10,000X and 144 were treated with viosterol and pollen injections.

2. Of the first group, 82.4 per cent experienced definite significant relief; 96.5 per cent of the second group had comparable degrees of relief. Thus 92 per cent of the entire series were definitely and significantly relieved.

3. The combined treatment of viosterol and pollen injections is more effective than either one alone.

4. The nature of the protective action of viosterol is undetermined, but is under further investigation. It does not seem to be related to the calcium mobilizing power of viosterol.

5. The optimum dose of 10,000X viosterol along with pollen injection for pollen sensitivity is between 2 and 10 drops daily, varying with the susceptibility of the individual rather than with the severity of the symptoms.

The viosterol 10,000X used for this work was supplied for experimental purposes only and is not at present commercially available.

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EXPERIMENTS IN SILK HYPERSENSITIVITY AND THE INHALATION OF ALLERGEN IN ATOPIC DERMATITIS (NEURODERMATITIS DISSEMINATUS)

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IT HAS long been known that atopic dermatitis (disseminated neurodermatitis) must be differentiated from eczematous dermatitis of the contact type, commonly called eczema. Sulzberger, Spain, Sammis, and Shahon[1] called attention to the fact that one of the most important differences between these two types of skin allergies is that the atopic dermatitis generally has many positive immediate wheal reactions and, in general, negative patch tests; while, in contact dermatitis, on the other hand, the reverse is true.

It was interesting to observe that, even in cases of atopic dermatitis without any respiratory symptoms whatsoever, in addition to foods, inhalant substances very frequently gave strongly positive immediate wheal reactions. This observation called attention to a possibility which, it seems, has not been sufficiently considered in connection with atopic skin hypersensitivity, or with skin sensitizations in general. For it is obvious that substances in the air may be absorbed through the respiratory tract, and thus enter the blood stream and reach the skin. If the absorption is through the lungs, the route to the skin is certainly shorter and more direct and without as much possibility of the denaturization of the allergen as is the case when absorption occurs through the gastrointestinal tract.

The inevitable conclusion from this is that inhalants must be considered as possible causes of sensitization dermatoses, with suspicion at least equal to that which is directed toward foods. If, in a given case of atopic skin hypersensitivity, both certain foods and certain inhalants have elicited positive skin reactions, the respective representatives of both groups must be eliminated, or the patient must be hyposensitized to both inhalants and foods, before one can expect a complete therapeutic result; or before one is justified in assuming that the positive skin tests have no bearing upon the etiology of the dermatosis.[2, 3]

Those who have studied atopic dermatitis (for instance Taub and Zakon[4]; Figley and Parkhurst[5]) and we ourselves have observed nu-

merous cases in which the wearing of silk clothing and even the vicinity of silk caused exacerbations of the skin condition; in such cases the immediate wheal reaction to silk was generally strongly positive, the patch test with silk almost universally negative, at least so far as the typical eczematous epidermal response was concerned. The most plausible explanation of this phenomenon seems to be that the silk allergen is absorbed in the blood stream of the patient and disseminated to the (vascular) hypersensitive areas of the skin, or in some way reaches the actual superficial blood vessels before it can elicit a reaction. While it is possible that in the wearing of silk some of the allergen may be absorbed through the skin, a sufficient quantity penetrating the epidermis and reaching the blood vessels of the cutis (and we have seen cases in which this mode of absorption apparently took place, particularly through the follicles when the patient perspired), it is at least equally possible that silk particles could be absorbed through the respiratory tract.

The following experiments were carried out to substantiate the latter possibility. Patient L. F., aged twenty-six years, was selected as the donor of the serum with which the modified Prausnitz-Küstner experiments, described below, were carried out. The family history of the patient was positive for asthma and hay fever. She had had atopic dermatitis since the age of three years, with exacerbations and remissions. At the age of fourteen years, the eruption became generalized and persistent and was severe and continuous from the age of nineteen years to the present. There were occasional attacks of asthma (at the time of getting a shampoo, etc.) and sneezing fits in the mornings. There was also a history of gastrointestinal upsets, as well as of urticaria and angioneurotic edema. *The patient knew that the wearing of silk clothing caused her dermatosis to become aggravated, and that her condition improved when silk was avoided.* At the time of first examination, she presented a severe lichenified form of atopic dermatitis (neurodermatitis disseminatus), with involvement of the cubital areas, wrists, face, neck, etc. The picture was classic in appearance and localization. Skin tests for immediate wheal reactions were positive for various foods (wheat, carrot, coffee, ginger, rhubarb), and slightly positive to many other foods (milk, yeast, cheese, nuts, etc.). Oidiomycin Lederle (1:100) gave a definite wheal reaction, while trichophytin Lederle (1:30) was negative; among the inhalants, furs and feathers elicited positive tests; but the outstanding reaction was that to silk. The test with a 1:50,000 dilution of silk allergen extract (Arlington) was strongly positive, on several occasions causing a systemic reaction, as well as generalized flare-ups of the existing skin eruption on the days following. On account of the patient's extreme hypersensitivity to silk, and the severe exacerbations caused by injections of even 1:50,000 dilutions, hyposensitiza-

tion therapy had twice to be abandoned. *Contact tests revealed that there was no eczematous hypersensitivity to external contact with silk. The site to which concentrated silk allergen was applied as a patch test did not react in any way.* (This, at first glance remarkable finding, is the rule in atopic dermatitis.[1, 4, 5]) Patch tests with 24 common external eczematogenous substances were all negative, with the exception of slightly papulopustular irritations at the sites of three metallic salts (sodium arsenate, bichloride of mercury, and sodium dichromate).*

The classic Prausnitz-Küstner test showed that there was a high titer of silk reagins in the patient's serum. Passive transference to other allergens was not attempted.

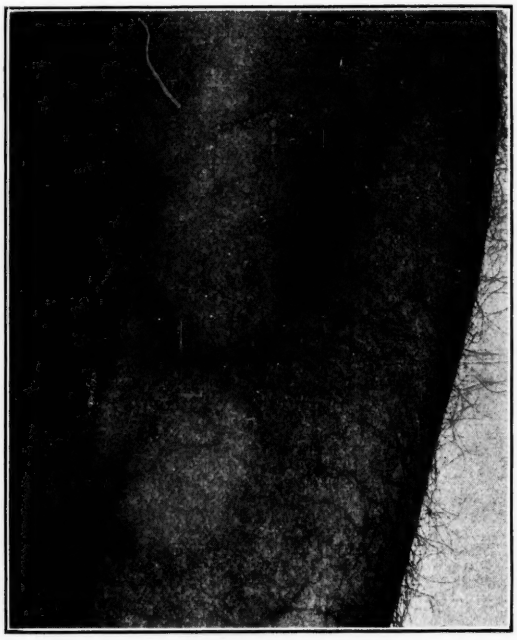

Fig. 1.—Wheals at the two sites passively sensitized with the silk reagin serum of L. F. (neurodermatitis), as they appeared forty minutes after the test individual inhaled silk allergen.

Experiment I.—One-tenth c.c. of serum of L. F. was intradermally injected into each of two areas on the left forearm of a nonatopic and non-silk-hypersensitive individual. Serum from a normal control person, nonatopic and nonhypersensitive to silk, was correspondingly injected into two corresponding areas on the right forearm of the test person. Forty-eight hours later, the test person sniffed a small amount of the Arlington Chemical Co.'s powdered silk allergen into each nostril

*We wish to remark that, while atopic dermatitis is generally negative to patch tests with most external eczematogenous agents,[1] this does not apply to salts of the heavy metals. We have seen the above described reaction quite often in classic atopic dermatitis. Particularly the nickel sulphate site is frequently occupied by a slight irregular streaky erythema and a few papulopustules. The significance of this reaction (which is not a typical eczematous response) is, as yet, unknown.

(unfortunately, the amount of allergen was not weighed, but a liberal pinch was taken into each nostril, as in taking snuff; we did not weigh the allergen, as we were here interested simply in the demonstration of a principle rather than in a quantitative experiment). Approximately eighteen minutes after sniffing, the two L. F. serum sites (on the left arm) began to itch so severely that it was difficult for the test person to refrain from scratching. A slight redness then began to appear and, at twenty minutes, a small but distinct wheal and an areola of erythema were visible at each of the atopic serum sites. The itching, the size of the wheal, and the erythema increased progressively. At thirty-five minutes after sniffing, two wheals, each approximately 2 inches in diameter, surrounded by a vivid erythema occupying the major part of the forearm, could be observed at the sites previously treated with the atopic serum (Fig. 1). The itching had increased in intensity. Forty minutes after sniffing, the reactions began to diminish, and the itching to abate. However, even after two hours, there was still a definite thickening of the skin to be palpated at the wheal sites. Twenty-four hours later, the sites previously occupied by the wheal and erythema showed a slight brownish pigmentation and felt slightly sore, like a mild bruise, when touched.

The two sites on the right arm (previously treated with the normal serum) did not react either subjectively or objectively, at any time during the experiment.

Two days later, silk allergen was again sniffed by the test person. No reaction was elicited. Furthermore, the application of silk allergen as a scratch test at the serum sites caused only a slight response. (This would seem to indicate that the first reaction, caused by sniffing, had been almost complete; i.e., had nearly exhausted the reagins.)

Experiment II.—Two weeks after the completion of Experiment I, the left and right forearms of the same test persons were injected with normal and with atopic serum, two sites on each arm, in the manner described in Experiment I. The serums, however, were not injected into the exact sites occupied by the previous injections. Twenty-four hours after the injection, patch tests with Arlington Chemical Co.'s silk allergen were applied to the previously treated sites, and allowed to remain in place for twenty-four hours. These applications consisted of a very high concentration of allergen, for the powdered silk allergen was simply moistened to form a thick paste, and then applied. After a lapse of thirty-five minutes, a slight itch was felt at the site of the patch test which had been applied to one of the areas previously injected with atopic serum. At the end of fifty minutes, the itching having persisted, the patch test at this site was removed for a moment, and a small wheal about one-half inch in diameter was

seen. The patch test was reapplied and the itching ceased within the next ten minutes. All four patches, including the reapplied patch, were allowed to remain in place twenty-four hours. *No eczematous reaction was elicited at any of the patch test sites*, although a slightly elevated erythematous plaque was seen only at the site of the patch test which had itched. This makes it probable that small quantities of silk allergen were continually penetrating the epidermis in this area, as long as this patch test remained in place; and that this penetration of allergen to the vascular layers maintained a continual slight degree of whealing.

The other site prepared with atopic serum and the two normal serum sites showed no reaction at any time during this experiment. After completion of the above described experiment, application of silk allergen to a scratch test at the four sites elicited a strongly—apparently maximum—positive wheal and flare reaction at both atopic serum sites. This indicates that the absorption of silk allergen through the epidermis from the patch test had been insufficient to cause a complete reaction and resultant exhaustion of the reagins. As was to be expected, the normal serum sites did not react to the scratch tests.

A repetition of Experiments I and II on a second test individual gave results identical with those described.

The results of these inhalation experiments coincide with those of Cohen et al.,[6] with the elicitation of passive transference reactions with serums from cases of ragweed hay fever, by means of inhalation of ragweed pollen allergen by the test individual. Our experiments are, however, apparently the first to be undertaken with this method and employing serum coming, not from a case of respiratory idiosyncrasy, but from an atopic dermatitis. It seems to us that they demonstrate that the *inhalation* of allergen (and *inhalant allergens*) can elicit skin reactions in individuals whose skin is equipped with the specific Prausnitz-Küstner antibody.

The second experiment suggests that *the penetration of allergen through the intact epidermis, while possible, is not very rapid*, even under the most favorable conditions. This would help explain both the fact that patch tests with silk were negative in our case, and that this is the rule with patch tests in atopic dermatitis.[1, 4, 5] Furthermore, atopic dermatitis has its favorite localizations and appears regularly in those favored areas, and usually regardless of the sites of external contact with the offending excitants. For instance, our patient, on wearing silk stockings, had exacerbations of the atopic dermatitis, not on the legs or feet, at points of contact, but in the cubital spaces and on the face and neck. This speaks rather in favor

of inhalation and hematogenous distribution as a route of access to the cutaneous vessels. This is possibly more important in adults than in infants, in whom the epidermis seems to be more permeable to substances coming from within or without.*

From what has been said at the beginning of this paper, it is clear that many patients with atopic dermatitis fulfill the requirement of having atopic inhalant-reagins in their skin. Obviously, the donor of the serum, L. F., who had an abundance of silk reagins in her serum, and who had an extreme skin hypersensitivity of the immediate wheal type to direct silk tests, must have had some degree of reaction when blood-borne silk allergen reached hypersensitive cells of the skin blood vessels. Even if the small quantity constantly and inevitably inhaled were not sufficient to cause actual whealing, it might very well have sufficed to cause itching (there was very severe itching in Experiment I, even preceding the appearance of the wheal). Minute amounts of inhaled silk allergen repeatedly, persistently, and chronically reaching the hypersensitive skin areas could very well lead, by constant repetition of subclinical reactions, to the final thickened, pigmented, lichenified lesions of the classic atopic dermatitis. Or, such repeated reactions might cause no more than persistent itching; and the consequent scratching and trauma could, as Brocq and others have supposed, be the actual cause of the ultimate lichenified skin lesions.

We report these experiments, not with the intention of affirming that they prove that inhalation of allergen is the actual mechanism in all cases of atopic dermatitis, nor that inhalants or silk are the main causes of this dermatosis, but simply as additional evidence that inhalants and the respiratory route of absorption must be seriously considered in the future studies of the pathogenesis of atopic dermatitis, of urticarias, of prurigo mitis, of some forms of infantile eczemas, and perhaps even of some eczematous eruptions of the type known as contact dermatitis. (For the hematogenous pathogenesis of eczematous eruptions of the contact type, see References 7 and 8.)

For the present, we should like to deduce from these experiments only that for the study of atopic dermatoses and for the evaluation of the possible significance of the skin tests in these conditions it would seem that allergen-free rooms are just as essential as elimination diets; and that elimination of or hyposensitization with inhalant substances, combined with the elimination of and hyposensitization with food allergens, is necessary before reaching the conclusion that a positive skin test is of no clinical significance in atopic dermatoses.

*Experimental studies of this possible difference in the permeability of infant and adult skin are in progress.

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STUDIES ON POLLEN AND POLLEN EXTRACTS

XIII. Dextrose Pollen Extracts: Therapeutic Results in 1933* †

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IN A previous paper[1] which described a new extracting solution for pollens, namely 5 per cent dextrose, the reasons for the study were pointed out. Up to that time the various extracting fluids were found to have certain faults. Pollen extracts made with saline solutions with or without the addition of ethyl alcohol are relatively unstable. Glycerin or glycero-saline extracts are quite stable and give excellent results therapeutically; there is no doubt of their efficiency and many reports of good results from their use are in the literature. One of the latest is by Aaron Brown[2] who found that 50 per cent glycerolated ragweed extracts gave much better results in 1932 in 51 cases than were obtained in these same cases in 1931 with aqueous extracts; in addition, constitutional reactions were not so severe with the glycerolated extracts, though as frequent.

It was pointed out, however, in our previous paper[1] that solutions containing glycerin cause considerable pain on injection; that they cannot well be used in concentrated solutions for intradermal testing nor are they suitable for intradermal testing if the diluting fluid contains glycerin; and that the high viscosity of the glycerin makes it quite difficult to force the extract through fine needles, especially the 27 gauge needles used in our work.

It was shown by us that the extract of mixed ragweed pollens in cresolized 5 per cent dextrose solution is about as stable as is the glycero-saline extract; that it is much less painful; that it can be drawn through fine needles; and that it can be used for intracutaneous testing as well as for treatment. It was also pointed out that comparative skin tests on hay fever patients and on rabbits gave no essential difference between the two. In that paper also there was included a preliminary report of its therapeutic results in 1932; this showed that the dextrose and the glycero-saline extracts gave about equal clinical results and had about an equal number of systemic reactions.

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TABLE I

THERAPEUTIC RESULTS IN 1933

NAME	AGE	SEX	DURATION (YEARS)	YEARS OF TREATMENT	DIAGNOSIS	D. P.	G. S.	PERENNIAL	PRESEASON	NO. OF INJECTIONS	REACTIONS	RESULTS
H. T.	45	F	7	2	Rag. & Dust A. (Per)	x		x		38	0	Exc.
M. C.	35	F	10	1	Rag. H. F. & Asthma	x		x		46	1	Imp.
H. B.	38	M	30	1	Rag. H. F. & Asthma	x			x	32	2	Good
S. F.	37	F	28	4	Rag. & Gr. H. F. & A.	x		x		33	0	Imp.
R. M.	31	F	3	2	Rag. H. F. & Asthma	x		x		31	0	Exc.
D. O.	13	M	5	1	Rag. H. F. & A. (Egg A.)	x		x		36	0	100%
S. R.	35	F	4	1	Rag. H. F.	x			x	40	0	Exc.
G. R.	42	F	20	1	Rag. & Grass H. F.	x			x	44	1	Imp.
J. S.	9	M	5	3	Rag. & Grass H. F.	x		x		27	1	Good
A. W.	21	M	15	2	Rag. H. F.	x		x		31	0	Good
L. A.	13	F	6	2	Rag. & Grass H. F.	x			x	28	0	Exc.
F. A.	38	M	4	1	Rag. H. F. & A.	x			x	48	0	Exc.
M. A.	26	F	6	3	Rag. Gr. Tr. H. F. & A.	x			x	35	1	Worse
A. A.	28	M		3	Rag. & Gr. H. F. & A.	x			x	29	0	Imp.
W. A.	27	F	10	1	Rag. & Gr. H. F. & A.	x			x	33	0	Same
H. B.	36	M	31	9	Rag. H. F. & Asthma	x		x		28	0	Good
H. B.	5	M	4	1	Rag. H. F. & Asthma	x		x		26	0	Exc.
V. B.	31	F	16	4	Rag. H. F. & Asthma	x		x		40	3	Good
N. B.	26	M	2	1	Rag. H. F.	x			x	40	0	Same
D. B.	17	F	2	2	Rag. H. F.	x		x		30	0	Good
S. B.	15	M	7	3	Rag. & Grass H. F.	x		x		26	0	100%
R. B.	36	F	23	1	Rag. H. F. & A. (Egg A.)	x		x		29	0	Good
W. B.	25	M	7	1	Rag. H. F. & A-Dust A.	x			x	56	0	Good
S. C.	36	F	20	4	Rag. H. F.	x		x		29	2	Same
W. C.	38	M	27	1	Rag. & Gr. H. F. & A.	x			x	61	0	Same
W. C.	41	M	33	2	Rag. H. F. & Asthma	x		x		32	1	Good
H. C.	23	M	14	12	Rag. & Gr. H. F. & A.	x		x		27	0	100%
H. D.	19	M	18	5	Rag. H. F.	x		x		31	0	Imp.
S. E.	15	F	3	1	Rag. H. F.	x			x	35	0	Same
S. F.	9	M	5	4	Rag. H. F.	x		x		28	0	Exc.
H. F.	26	F	13	2	Rag. H. F. & A.	x			x	35	0	Good
A. G.	49	F	8	4	Rag. H. F. & A.	x		x		28	0	Same
R. G.	40	F	10	1	Rag. & Gr. H. F. & A.	x			x	39	0	Good
M. G.	29	M	8	6	Rag. H. F.	x		x		29	1	Good
P. G.	11	M	6	2	Rag. & Gr. H. F.	x		x		30	0	Exc.
W. H.	16	M	1	1	Rag. H. F.	x			x	33	0	Exc.
C. H.	31	M	4	3	Rag. H. F.	x		x		20	0	Exc.
J. H.	29	M	28	1	Rag. A. & Per. A.	x			x	48	0	Worse
B. H.	19	F	4	1	Rag. & Grass H. F.	x			x	38	0	Imp.
H. H.	77	M	11	2	Rag. H. F. & A.	x		x		34	0	Good
R. H.	10	M	3	1	Rag. H. F.	x			x	34	0	Good
R. H.	19	M	5	2	Rag. & Gr. H. F. & A.	x		x		32	0	Same
N. H.	11	F	10	3	Rag. & Gr. H. F. & A.	x		x		23	0	Exc.
T. H.	49	M	20	10	Rag. H. F. & A.	x			x	35	0	Imp.
M. H.	25	M	2	1	Rag. H. F. & A.	x			x	35	0	Good
F. K.	13	M	8	5	Rag. H. F.	x		x		31	0	Good
J. K.	40	M	7	6	Rag. H. F. & A.	x		x		29	1	Good
M. K.	16	M	11	4	Rag. H. F. & A.	x		x		27	1	Exc.
L. K.	30	M	11	2	Rag. & Gr. H. F. & A.	x			x	32	0	Imp.
C. K.	12	M	3	2	Rag. & Gr. H. F.	x		x		32	0	Good
C. Y.	20	M	16	3	Rag. H. F. & A.	x			x	35	3	Good
C. W.	17	M	15	1	Rag. H. F. & A.	x			x	40	0	Imp.
C. W.	22	M	6	2	Rag. H. F.	x		x		31	1	Same
D. W.	6	M	2	1	Rag. H. F.	x			x	32	0	Good
C. W.	21	F	16	4	Rag. H. F.	x		x		28	0	Exc.

Rag. = ragweed. Per. = Perennial. D.P. = dextrose-phenol Exc. = excellent.
A. = Asthma. H.F. = Hay fever. G.S. = glycero-saline. Imp. = improved.

TABLE 1—CONT'D

NAME	AGE	SEX	DURATION (YEARS)	YEARS OF TREATMENT	DIAGNOSIS	D. P.	G. S.	PERENNIAL	PRESEASON	NO. OF INJECTIONS	REACTIONS	RESULTS
A. V.	26	F	8	4	Rag. & Grass H. F.	x			x	57	0	Good
F. V.	39	M	4	4	Rag. H. F.	x		x		33	0	Good
L. T.	11	M	3	1	Rag. & Grass H. F.	x			x	43	0	Imp.
N. S.	6	F	3	1	Rag. & Gr. H. F. & A.	x			x	26	0	Imp.
W. S.	37	M	16	5	Rag. H. F. & A.	x		x		30	0	Good
J. S.	34	F	10	2	Rag. H. F.	x		x		31	0	Good
I. S.	22	F	16	4	Rag. & Gr. H. F. & A.	x		x		32	1	Imp.
R. R.	58	M	7	4	Rag. H. F. & A.	x		x		32	0	Exc.
I. R.	30	F	25	2	Rag. H. F. & A.	x		x		32	2	Exc.
O. R.	48	F	35	4	Rag. H. F.	x		x		10	0	Exc.
E. R.	40	M	16	2	Rag. H. F. & A.	x		x		31	1	Exc.
D. R.	7	M	4	3	Rag. & Gr. H. F. & A.	x		x		26	0	Imp.
I. P.	19	F	5	4	Rag. & Gr. H. F.	x		x		30	0	Imp.
M. P.	7	M	3	2	Rag. & Gr. H. F. & A.	x		x		26	0	Good
J. M.	18	M	5	1	Rag. H. F. & A.	x			x	35	5	Good
N. M.	13	M	6	3	Rag. & Gr. H. F.	x		x		24	0	Exc.
D. L.	4	M	3	2	Rag. & Grass H. F.	x		x		25	0	Good
O. L.	21	F	7	1	Rag. H. F.	x			x	33	0	Same
N. B.	29	M	27	4	Rag. H. F. & A.	x			x	26	0	Imp.
H. B.	41	F	14	3	Rag. H. F. & A.	x		x		22	0	Imp.
J. B.	26	F	4	1	Rag. H. F. & A.		x	x		31	0	Imp.
J. B.	43	M	15	1	Rag. & Gr. H. F. & A.		x		x	28	2	Good
M. C.	4	M	3	2	Rag. & Gr. H. F. & A.	x		x		31	0	Exc.
V. C.	14	F	5	1	Rag. H. F. & A.	x		x		28	0	Imp.
A. D.	48	M	4	3	Rag. H. F. & Per. A.		x	x		34	0	Good
L. D.	7	M	4	2	Rag. H. F. & Per. A.		x	x		27	0	Exc.
B. D.	42	F	12	1	Rag. & Gr. H. F. & A.	x			x	33	1	Imp.
M. G.	33	F	25	3	Rag. & Gr. H. F. & A.	x		x		20	0	Same
C. G.	22	M	3	2	Rag. H. F. & A.		x		x	27	0	Good
M. H.	45	F	14	3	Rag. H. F. & A.		x	x		24	0	Imp.
A. H.	32	M	20	2	Rag. & Gr. H. F. & A.	x		x		47	3	Imp.
H. H.	40	F	18	1	Rag. H. F.	x		x		25	1	Imp.
A. H.	10	M	6	1	Rag. H. F.		x	x		26	0	Imp.
C. H.	14	F	14	1	Rag. & Gr. H. F. & A.		x	x		30	0	Good
L. O.	46	F	15	3	Rag. H. F. & A.		x	x		23	0	Exc.
A. N.	34	F	4	3	Rag. H. F. & A.		x	x		26	0	Good
R. M.	13	M	2	1	Rag. H. F. & A.	x			x	33	0	Good
E. M.	40	F	2	1	Rag. & Gr. H. F. & A.	x		x		37	0	Good
H. M.	47	F	8	2	Rag. H. F. & A.	x		x		27	1	Good
I. K.	6	M	2	2	Rag. H. F. & A.		x	x		18	0	Good
L. K.	45	M	5	3	Rag. Gr. Tree H. F.		x	x		23	0	Exc.
A. K.	35	M	4	3	Rag. H. F. & A.		x	x		13	0	Exc.
F. W.	42	M	3	1	Rag. H. F. & A.		x	x		42	0	Imp.
A. V.	34	F	8	1	Rag. H. F. & A.	x		x		43	0	Same
M. V.	45	F	19	4	Rag. H. F. & A.		x		x	27	1	Imp.
C. T.	58	M	33	1	Rag. H. F. & Per. A.	x			x	30	0	Imp.
A. T.	42	M	7	2	Rag. H. F. & Per. A.		x	x		21	0	Same
C. S.	32	M	5	1	Rag. H. F. & A.	x			x	22	0	Good
S. S.	27	F	10	2	Rag. H. F.	x		x		22	0	Good
R. S.	32	F	13	3	Rag. H. F. & A. Gr. H. F.	x		x		26	3	Good
J. S.	10	M	6	3	Rag. H. F. & Per. A.	x		x		16	0	Good
J. S.	40	F	16	2	Rag. H. F. & Per. A.		x	x		36	2	Same
P. R.	13	F	4	1	Rag. H. F.	x			x	21	0	Imp.
D. R.	42	M	15	1	Rag. H. F. & A.	x		x		43	0	Same
F. R.	13	M	10	3	Rag. & Gr. H. F.		x	x		21	0	Same
H. P.	13	M	2	1	Rag. H. F.	x			x	21	1	Imp.
M. C.	30	F	10	3	Rag. & Gr. H. F.	x		x		25	0	Same
H. S.	29	F	13	2	Rag. H. F.	x			x	22	0	Imp.

PREPARATION OF DEXTROSE POLLEN EXTRACTS

Three grams of pollen are extracted with 100 c.c. of the extracting fluid (an aqueous solution containing 5 per cent dextrose and 0.5 per cent phenol; the extracting fluid previously reported contained 0.1 per cent cresol instead of the phenol). After filtration through paper the extract is filtered through a Seitz or Berkefeld filter, incubated for three days and refrigerated for about a week, or until a precipitate has formed. This precipitate consists of an inactive glucoside. The extract, if cloudy, is again filtered through a sterile filter and is kept under observation for about two weeks to see whether the precipitation is complete. If not, it may be refiltered with practically no loss in potency. After the final filtration the extract is, of course, tested for sterility.

Studies were made on both clinic and office patients suffering with ragweed hay fever with or without asthma; some were complicated by other sensitizations such as grass pollen hay fever.

Therapeutic results in 1933 are shown in Table I.

In all, 113 patients were studied, 40 from the Hay Fever Clinic and 73 from private practice. These were carefully followed, and they cooperated in their treatments so that accurate results could be established. Others who reported late, who were irregular in attendance, or who failed to keep up the injections are not included.

TABLE II

Ragweed hay fever	26
Ragweed hay fever and asthma	42
Ragweed and grass hay fever	14
Ragweed and grass hay fever and asthma	21
Ragweed hay fever and perennial asthma	8
Ragweed, grass and tree hay fever	1
Ragweed, grass, tree hay fever and asthma	1
	113

Table II merely represents the varieties of ragweed cases seen. It is interesting to note that only 26 of the 113 were uncomplicated ragweed hay fever victims. Perhaps this small percentage indicates that this group does not so often seek medical attention. The large number of asthmatic individuals (74 out of 113) is also noteworthy, and the good results obtained in this group are very encouraging.

Table III shows that 18 of the 113 cases were treated by the glycerosaline extracts of ragweed pollen, prepared in the usual way; all of these were clinic cases. The remaining 95 were given injections of dextrose-phenol extracts; 22 of these patients were from the clinic and 73 from the office. In all other particulars, the technic, number of doses, etc., were similar in the two groups.

TABLE III

THERAPEUTIC RESULTS OF RAGWEED CASES, 1933

	GLYCERO-SALINE		DEXTROSE	
	NO.	PER CENT	NO.	PER CENT
100%	--	--	3	3.1
Excellent (90-95%)	4	22.2	19	20.0
Good (50-75%)	6	33.3	34	35.8
Improved (25-50%)	5	27.7	24	25.2
Same	3	16.6	13	13.6
Worse	--	--	2	2.1
Total cases	18	99.8	95	99.8

The figures are remarkably similar for the two groups, and it was gratifying to be able to obtain as good success as we did when one realizes that 1933 was one of the worst, if not the worst, hay fever season known. Mr. O. C. Durham[3] found the ragweed pollen count, in Chicago, for 1933 was 7,214, as opposed to 6,020 in 1932. Table III shows that we obtained from 83 to 85 per cent of improved, good, or excellent results. This is better than previously found and is possibly due to two factors: (1) The injections were pushed higher and many of the patients, especially the private ones, were given 3 per cent extracts instead of 1 per cent. (2) All patients were routinely tested for pollens and nonpollen proteins, a practice we have carried out for several years; proteins giving positive reactions were eliminated as far as possible during the hay fever season. We think that this is a valuable procedure.

CONSTITUTIONAL REACTIONS

In the matter of constitutional reactions varying from mild to severe hay fever, asthma, or urticaria or combinations thereof, five such reactions occurred in the 18 patients treated with glycero-saline extracts. As there were 477 injections in this group, the percentage of reactions to injections equals 1.03 per cent. In the dextrose group of 95 patients there were 38 reactions which followed 3,035 injections, or a total of 1.2 per cent. It is seen, therefore, that there was a slightly higher percentage of reactions in the dextrose group. This fact is hard to explain. Perhaps the glycerin allows slower absorption of the pollen extract, although Aaron Brown[2] found as many reactions in his glycerine group as in the aqueous-treated patients. In our series we believe that the answer may lie, in part, in the fact that the dextrose group, as a whole, received stronger extracts than the other. None of the reactions were serious but their frequency certainly demands great care in increasing the dosage.

PERENNIAL VS. PRESEASONAL TREATMENT

In a previous paper[1] the advantages of the perennial treatment of hay fever were pointed out. These have also been stressed by a num-

ber of other observers. Table I shows that 73 of the patients were treated all year round; 40 were given injections before the season. The summary (condensed in Table IV) indicates that there was little to choose between these two methods as far as therapeutic results are concerned.

TABLE IV

THERAPEUTIC RESULTS

	GLYCERO-SALINE				DEXTROSE			
	PERENNIAL		PRE-SEASONAL		PERENNIAL		PRE-SEASONAL	
	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE
100%	0	0	0	0	3	5.2	0	0
Excellent	4	26.6	0	0	15	25.9	4	10.8
Good	5	33.3	1	33.3	20	34.4	13	35.1
Improved	3	20.0	2	66.6	11	19.0	13	35.1
Same	3	20.0	0	0	9	15.5	5	13.5
Worse	0	0	0	0	0	0	2	5.4
Totals	15	99.9	3	99.9	58	100.0	37	99.9

About 85 per cent of those treated perennially by dextrose extracts were improved or better. One striking finding here is that 25.9 per cent of the perennials obtained excellent results to only 10.8 per cent in the preseasonal group. The glycero-saline group was too small to compare perennial vs. preseasonal findings.

DISCUSSION

Recent tests, as yet unpublished, as to the stability of dextrose extracts are very interesting. We have carried out a series of intracutaneous tests on ragweed hay fever cases and have used samples of glycero-saline and dextrose pollen extracts. A portion of each was incubated and a part refrigerated for over two and one-half years. The reactions were about equal with the glycero-saline and dextrose extracts. There was, as was to be expected, a moderate loss of activity in the refrigerated samples and a considerable loss in the incubated ones. It was surprising that we were able to get four-plus reactions in some sensitive patients with extracts which had been kept continuously in an incubator for over thirty months. Similar results were obtained in grass pollen extracts incubated and refrigerated about sixteen months and tested on grass sensitive individuals.

These tests indicate to us the folly of discarding solutions each year. The extracts made either with glycero-saline or dextrose remain remarkably potent for at least thirty months, a period longer than any of us would ordinarily keep our extracts. As all of us increase our dosages in accordance with the tolerance of our patients the slight deterioration which occurs in all extracts merely calls for more

rapid increases in dosage in the older extracts. At the same time we must be very cautious when we change to new extracts. It is a simple matter to reduce the dosage and work up again. Such care will prevent many reactions.

We wish that more allergists would try the dextrose extracts. It is a pleasure to know that one of them, Dr. Peshkin, in a personal communication, has done a good deal of work along the line of comparative skin tests. He will, no doubt, report his own results.

In our work, both at the office and at the clinic, we now use only the dextrose extracts.

SUMMARY AND CONCLUSIONS

1. One hundred and thirteen patients with ragweed hay fever and asthma were treated with comparative injections of glycero-saline and dextrose extracts of ragweed pollen to determine the respective therapeutic value of these two methods.

2. The clinical results were about equal in the two groups; from 83 per cent to 85 per cent were improved, good, excellent, or had 100 per cent relief for the season of 1933.

3. In the glycerin group there were 1.03 per cent constitutional reactions; the dextrose cases showed 1.2 per cent.

4. On the whole, the perennially treated patients gave more excellent therapeutic results than did those who had preseasonal injections.

5. The high percentage of good results in 1933 is probably attributable to giving stronger injections than previously; and to avoidance of nonpollen positive reactors during the hay fever season.

6. Both glycerin and dextrose extracts are potent and stable and resist long incubation and refrigeration. There is, therefore, no need to discard extracts each year. Great caution must be exercised in changing from old to newly prepared extracts.

7. The dextrose pollen extract has the advantage of being much less painful, is better for intracutaneous testing and is easier to handle. We believe it is the best extracting and diluting fluid so far devised for pollen therapy.

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EXPERIMENTAL STUDY OF THE ETIOLOGY OF DERMATITIS VENENATA*

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IN A PRESENTATION before this Society in December, 1930, it was stated that newborn infants had been artificially sensitized to poison ivy.[1] This had been accomplished in one group by ingestion and skin application of a potent extract, and in another group by skin application alone in the form of a patch test. The sensitization of the skin, which was general, was indicated by a subsequent patch test with the same material after an interval of from two to four weeks. The results were positive in 72.9 per cent of 48 infants.

The present report deals with attempts at sensitization by ingestion alone and by subcutaneous injection of a solution of the active material.

Ten newborn infants were fed a 10 per cent solution of an alcoholic extract of poison ivy by placing two drops on the back of the tongue. This was repeated daily during the stay in the hospital. The average amount ingested by each infant was ten drops. The material was not vomited, nor were any untoward gastrointestinal symptoms observed. The infants were discharged at the usual time and after an interval of several weeks were tested with the ivy paste by the patch method. When observed one week later, the results of the patch tests were *negative* in all *ten* infants (Table I).

TABLE I

FEEDING IVY SOLUTION BY MOUTH, FOLLOWED BY CUTANEOUS PATCH TEST WITH IVY PASTE

CASE NO.	NAME	SEX	AMOUNT FED AT 2 DROPS PER DAY	INTERVAL SINCE LAST FEEDING	PATCH TEST APPLIED	DATE OBSERVED	RESULT
5	E	F	12 drops	None	8/31/30	9/ 3/30	0
6	V	M	14 drops	None	8/31/30	9/ 3/30	0
7	T	M	14 drops	None	8/31/30	9/ 2/30	0
8	G	M	14 drops	None	8/31/30	9/ 2/30	0
9	T	M	12 drops	25 days	9/26/30	10/ 3/30	0
10	L	F	10 drops	25 days	9/26/30	10/ 3/30	0
						10/10/30	0
12	M	F	8 drops	31 days	10/ 3/30	10/10/30	0
15	R	M	6 drops	31 days	10/ 3/30	10/10/30	0
						10/17/30	0
16	L	M	6 drops	31 days	10/ 3/30	10/10/30	0
17	L	M	4 drops	45 days	10/17/30	10/24/30	0

*Read before the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 30, 1932.

In another group of ten infants, 1 c.c. of a 10 per cent solution of the alcoholic extract (5 per cent—Coca), was injected subcutaneously into each infant. These infants were likewise tested by the patch method with the ivy paste after a suitable interval, and the results observed a week later. Nine infants gave a negative result and one infant a positive result. Although every precaution was taken to prevent the solution coming in contact with the epidermis, it is impossible to say with certainty that this did not occur in the sensitized case (Table II).

TABLE II

SUBCUTANEOUS INJECTION OF IVY SOLUTION, FOLLOWED BY PATCH TEST

CASE NO.	NAME	SEX	SUBCUTANEOUS INJECTION—1 C.C.	PATCH TEST	DATE OBSERVED	RESULT
1	S	M	10/21/30	11/14/30	11/21/30	0
					11/28/30	0
2	H	F	10/21/30	11/14/30	11/21/30	0
3	B	F	10/21/30	11/21/30	11/28/30	0
4	D	F	10/24/30	11/21/30	11/28/30	+++
5	R	M	10/24/30	11/21/30	11/28/30	0
					12/ 5/30	0
					12/12/30	0
6	B	F	10/24/30	12/ 5/30	12/19/30	0
7	C	F	10/30/30	12/ 5/30	12/12/30	0
					12/19/30	0
8	S	F	10/30/30	11/28/30	12/ 5/30	0
					12/19/30	0
9	W	F	10/30/30	12/ 5/30	12/19/30	0
10	S	F	10/30/30	12/ 5/30	12/12/30	0

The dosage in both the feeding and the injection cases was quantitatively calculated to be at least equal to the amount of active material applied to the skin in the successfully sensitized cases, described in the previous paper.[1]

The potency of the material was accidentally demonstrated when a nurse developed the typical lesions of poison ivy after carelessly handling the bottle containing the solution.

The failure to sensitize by feeding and the small percentage sensitized by injection of a potent solution of the ivy extract as compared to 72.9 per cent sensitized by cutaneous contact, seems to indicate that the best, if not the only way in which sensitization to poison ivy can be induced is by adequate cutaneous contact with the active principle.

Quite recently some of the infants successfully sensitized in the first study were recalled for retesting. They were then between eighteen and twenty months of age. Our purpose was to see whether their skin sensitivity was still present and at the same time to test the specificity of an extract of poison sumac, made in the manner of Coca's poison ivy paste.[1] Six infants were available and on each a patch test was done on the right arm with the ivy paste, and on the left arm with

the sumac paste. Patches were allowed to remain in place for three days and were then removed with benzene and the sites washed. One week after testing the results were read. Four of the infants responded with strongly positive reactions to both ivy and sumac. One infant while not developing the dermatitis had experienced itching as evidenced by scratch marks at both sites. In the remaining infant both sites were negative.

These results seem to indicate that there is a common principle in poison ivy and poison sumac. In the injection treatment of dermatitis from ivy or sumac, an extract of one could be used in the treatment of either.

SUMMARY

1. In the case of ten infants, the ingestion of a solution containing the active principle of poison ivy, did not result in sensitizing the skin.

2. In the case of ten other infants, who were subcutaneously injected with the extract, the skin was sensitized in only one case.

3. By cutaneous application of an ivy paste, the skin was successfully sensitized in 72.9 per cent of 48 infants.[1]

4. Artificially induced sensitization to poison ivy lasts a long time.

5. Those infants who gave positive reactions to poison ivy also gave positive reactions to poison sumac; although it is reasonably certain that at their age they had never had previous contact with sumac. The active principle in ivy and sumac therefore is immunologically identical.

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41 Eastern Parkway

DISCUSSION

Dr. A. F. Coca, Pearl River.—Dr. Straus' experiments seem to confirm the accepted view that the sensitivity of contact dermatitis is limited to the epidermis and does not affect the other tissues of the body. They also indicate that in the general sensitization of the skin the excitant is not distributed through the blood or lymph; hence the generalized cutaneous reaction which Dr. Straus observed after a local application of the extract of ivy to a single site must be explained by some other means of distribution, possibly by diffusion of the excitant through the oily substances normally present in the skin.

THE PERCENTAGE OF PERSONS SUSCEPTIBLE TO POISON IVY AND POISON OAK*

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IN THE course of an investigation of the sensitivity of adult patients to the skin irritants of poison ivy (*Toxicodendron radicans L.*) and of poison oak (*Toxicondendron toxicodendron L.*), it was noticed that the percentage of persons affected by different concentrations of these irritants varied in a definite mathematical manner.

The extracts used for testing were made as described previously,[1] that is, the dried leaves were extracted in absolute alcohol in the proportion of 10 c.c. of alcohol to one gram of dried leaf powder. This extract was not decolorized or treated further but diluted with absolute alcohol to 1:3, 1:10, 1:30, and 1:100. In the case of the ivy, a 30:1 concentration was made by rapidly evaporating 90 c.c. of the extract to 3 c.c. Patch tests of these were applied in the usual way.

On the first visit the 1:100 dilutions were applied to all the patients. They were instructed to leave the patch test in place for twenty-four hours, and the result was observed on the seventh and fourteenth days, to allow for differences in incubation periods,[2] when the patient returned. A reaction was considered positive when a lesion typical of ivy or oak poisoning was reproduced beneath the patch. Plus signs, with the usual interpretation, were used to describe the degree of reaction: local erythema and itching persisting for several days being considered as +. If at the end of a seven-day period no reaction was evident, the next stronger dilutions were applied. This process was continued, eliminating those patients who gave positive reactions to each dilution, until the strongest had been applied. The 1:3 dilution was omitted after the first few trials in order to shorten the length of the test. The results are shown in Table I.

For the sake of graphic study the reactions were classified as positive or negative without regard to the degree of the positive reactions. Since there was not a complete attendance on the part of the patients, some starting the test and not returning, allowance has to be made for this in the calculations. To do this, the percentage of those giving reactions to the weakest concentration was determined. This, subtracted from 100, gave the percentage of those immune. After the next exposure, the number of positive reactions obtained was divided by the number of tests applied, thus obtaining the proportion of sensitive persons at this

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strength of extract. The result was multiplied by the percentage immune before the exposure, and the product was subtracted from the latter percentage. By so doing the proportion of negative reactions at any one level was corrected into percentage of the original at the start of the study. The figure arrived at was the percentage of immunes to the dose tested. This could be subtracted from 100 to obtain the percentage of susceptibles as recorded in Table I. In this way, no matter how many patients failed to return for testing, the results are always adjusted to the basis of a hypothetical 100 patients attending regularly.

TABLE I

POISON IVY AND POISON OAK TESTS IN THE FALL OF 1933

CONCENTRATION	NO. OF PERSONS TESTED	NUMBER AND SEVERITY OF REACTIONS	TOTAL NUMBER POSITIVE	TOTAL % SUSCEPTIBLE
		POISON IVY REACTIONS		
1:100	101	8 (+), 9 (++), 8 (+++), 2 (++++)	27	27
1:30	69	9 (+), 3 (++), 1 (+++), 1 (++++)	14	42
1:10	54	2 (+), 2 (++), 1 (+++)	5	47
1:3	4	1 (+++)	1	
conc.	46	3 (+), 3 (++), 5 (+++)	11	60
30:1	32	12 (+)	12	75
		POISON OAK REACTIONS		
1:100	101	5 (+), 8 (++), 9 (+++), 2 (++++)	24	24
1:30	69	5 (+), 3 (++), 3 (+++), 1 (++++)	11	36
1:10	55	2 (+), 3 (++)	5	42
1:3	5	1 (+), 1 (+++)	2	
conc.	46	10 (+), 5 (++), 3 (+++)	18	65

The results have been plotted with percentage of susceptibles as ordinates against the concentration as abscissae, and also against the logarithm of the concentration. In the latter case a straight line is obtained, which means that the percentage of persons susceptible to these skin irritants increases uniformly as a given multiple of the concentration of the irritant. Thus, in the case of the poison oak, which had the best curve, tripling any given dose resulted in adding approximately 10 per cent of the population to those affected. This is in accordance with the action of drugs and of other physiologic stimuli in general as expressed in the Weber-Fechner law.[3]

The low value for poison ivy at the 30:1 concentration is probably due to some destruction of the active substance during the evaporation. We know of no method of checking the activity of poison ivy extract other than by biologic test. However, it is felt that the curve of the percentage of persons susceptible, plotted against the logarithm of the concentration, should continue as a straight line.

We have not noticed any peculiarity of the curve which might be attributed to a sensitization due to the first application of the extract,

except a very slightly high figure at the time of the second tests. All of our patients were adults and most of them had lived in the city. Many claimed never to have been exposed before to either poison ivy or poison oak.

Occasionally, when the tests had been applied several times in succession, in increasing concentration, without causing any reaction, a posi-

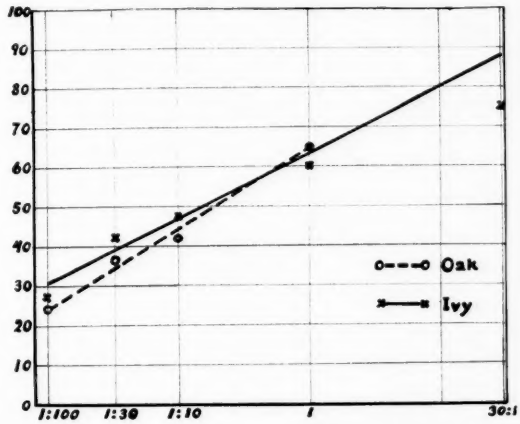

Fig. 1.—Percentage of persons susceptible as ordinates versus arbitrary units of irritant concentration plotted on a logarithmic scale as abscissae.

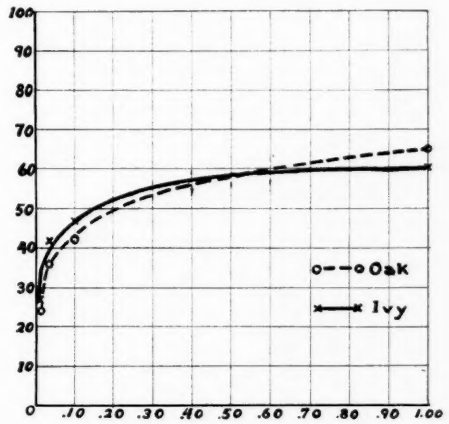

Fig. 2.—Percentage of persons sensitive as ordinates versus arbitrary units of irritant concentration as abscissae.

tive reaction would appear and one or more of the sites of previous tests would flare up simultaneously. In computing the results, these patients were classified in the group reacting to the stronger concentration at which the outbreak occurred rather than in the group in which the older reaction would be classified. It is to be supposed that the irritant stayed at the site for two or three weeks, and, when a sufficient amount had been applied, it was distributed from the new site to the older in such a

concentration as to set up a reaction. In one instance where several sites flared up, a typical reaction was observed at a place several inches away on the arm where a subcutaneous injection of ragweed pollen extract had been given for the treatment of hay fever at the time of the application of the last patch tests. Evidently the nonspecific irritation at the site of injection encouraged the production of the typical vesicular lesions.

CONCLUSIONS

Under equal conditions of exposure the percentage of adult human beings susceptible to the skin irritating action of poison ivy or of poison oak varies as the logarithm of the concentration of the irritant applied.

This is statistically similar to the action of drugs and other physiologic stimuli, in general, in agreement with the Weber-Fechner law.

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EXPERIMENTAL NICKEL DERMATITIS

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NICKEL dermatitis is a recognized and relatively common affection of the skin. The clinical reports on nickel dermatitis are summarized in recent publications by Goldman[1] and Stewart.[2] There is much speculation and little experimental evidence to determine the nature of the skin reaction with compounds of nickel. Conflicting conclusions cast doubt on much of the experimental work.

The purpose of this paper is to check the results of experiments previously published and to carry out further investigations. A review of the literature dealing with experimental nickel dermatitis will be briefly summarized as a background for the experiments to be presented.

Walthard[3] in 1926 noted that from 41 to 100 per cent of workers in the Swiss nickel industry developed nickel dermatitis. The dermatitis began after an incubation period of from fourteen to twenty-one days, and often spread beyond the exposed parts. He believed that the dermatitis might be a sensitization phenomenon and endeavored to verify this by animal experimentation with guinea pigs. He painted a 1 per cent solution of nickel sulphate several times daily on the clean-shaven hind legs of the animals. Pathologic changes appeared in the treated areas in the form of a typical nickel dermatitis in from fourteen to twenty-one days. When the painting was discontinued, the lesions quickly disappeared, but when the nickel solution was reapplied the dermatitis returned more quickly than before. He produced nickel dermatitis in six new pigs, following which an untreated area was painted. Dermatitis appeared in three days instead of twenty-one. He believed that this was proof of Jadassohn's theory of blood-carried sensitivity from within. He then injected 1 c.c. of a 1:1,000 solution of nickel sulphate subcutaneously into 15 animals with healing nickel lesions. In 11 there was a definite focal flare-up. Repeated subcutaneous injections in sensitized (?) pigs were alleged to produce a desensitization. The Prausnitz-Küstner phenomenon could not be produced and repeated intradermal injections into the pretreated (sensitized) areas failed to produce local reactions.

Jadassohn and Schaaf[4] endeavored to duplicate Walthard's findings in human beings. They made daily applications of solutions of nickel

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sulphate, percutaneously, for as long as 282 days. The strength of the solution was gradually increased from 1 to 20 per cent, but the only reaction observed was a local "irritative" type of dermatitis. They were unable to produce definite evidence of specific sensitivity to nickel.

Coca and Milford[5] in an unpublished series of experiments tried to produce nickel dermatitis in guinea pigs with solutions of nickel and cobalt chlorides. They were unable to produce specific sensitivity to nickel or cobalt.

Wilhelm and Milbradt[6] presented further experiments on nickel sensitization. White mice were used because of previous success in the production of experimental arsphenamine dermatitis in these animals. A 1 per cent nickel sulphate solution was used in three series of mice. In the first series applications were made on normal skin; in the second, the skin was first abraded with glass paper; and in the third, the skin was softened with a 30 per cent solution of potassium hydroxide. In a similar series 20 per cent nickel sulphate was used. Of the animals treated with a 1 per cent solution, 20 per cent died and many developed a severe anemia. The lesions were more intense in those animals traumatized with potassium hydroxide and glass paper, and were of an ulcerative type unlike the lesions of clinical dermatitis. When 20 per cent nickel sulphate was used, the changes were more severe. All those traumatized with potassium hydroxide and glass paper died. In the other animals, erythema, scaling, and infiltration occurred in from three to six weeks. When the treatment was continued, the changes went on to necrosis. After a period of from twenty-one to forty days, to allow for the development of sensitivity, 20 per cent nickel sulphate was reapplied. A reaction suggesting sensitivity occurred in 90 per cent of the cases. When applications were resumed after a short rest period, there was an exacerbation of the preexisting lesions. After from two to four months of continuous treatment the milder reactions became stationary and finally disappeared. When the ears of mice were treated separately with a nickel sulphate solution with an interval of twenty-one days to allow for the development of sensitivity, the later eruption was less intense. He concluded that generalized sensitivity was suggested by occasional experiments, but that in the large majority of animals the sensitization was purely a local phenomenon.

It is not surprising that these reports are conflicting and inconclusive, for great difficulty has been encountered in every attempt at sensitization that has been made with the various heavy metals.

EXPERIMENTAL DATA

In the following experiments various aspects of the reaction of nickel with the skin have been investigated. Guinea pigs have been chosen for these experiments primarily because of the ease with which specific sen-

sitization can be produced, and because in previous experimental work guinea pigs have been used in an effort to demonstrate nickel sensitization.

Experiment 1. Nickel dermatitis was produced in three groups of normal, medium-sized, young guinea pigs. Two per cent, 10 per cent, and 20 per cent solutions of nickel chloride were used. The chloride was used in preference to the sulphate of nickel because of its greater solubility. The nitrate was demonstrated to be too irritating to the skin when it was used for patch testing in patients with nickel dermatitis[2] Percutaneous applications of nickel chloride were made daily over the same area for one-half hour. The solution was applied by saturating small strips of gauze and fastening them in place on the abdomen of the guinea pigs. The abdomen had been denuded of hair several days previ-

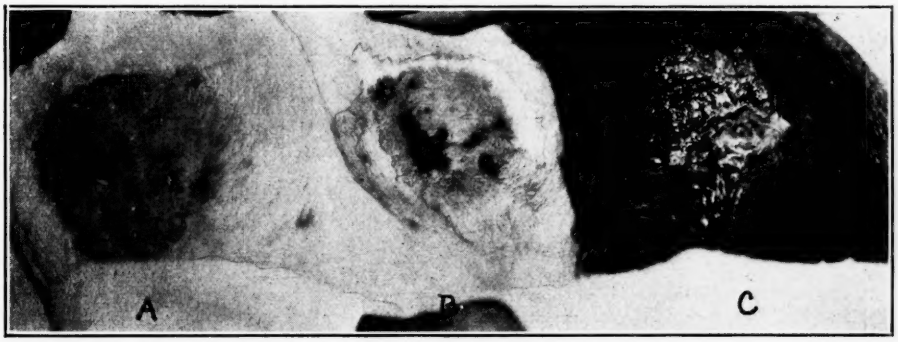

Fig. 1.—*A* represents an early, *B* a moderately advanced, and *C* a severe late reaction to percutaneous applications of 10 per cent nickel chloride on the abdomen of normal guinea pigs.

ously with a paste consisting of equal parts of barium sulphide and starch in water.

In a group of eight guinea pigs on which 2 per cent nickel chloride was used percutaneously, a slight erythema appeared on the second day. A definite papular eruption appeared on the fifth day and increased moderately in intensity. The eruption gradually subsided after the sixteenth day and disappeared completely, in spite of continued applications for ten more days.

Percutaneous applications with a solution of 10 per cent nickel chloride were made in a series of eight normal guinea pigs. A slight erythema was noted in twenty-four hours. On the third day it became more severe, with local edema, papules, and a scratch dermatitis from associated pruritus. After ten days the lesions persisted, with necrosis, crusting, deep fissures, and hemorrhage. After four weeks the lesions had become so ulcerated and hemorrhagic that applications of nickel were discontinued.

A 20 per cent solution of nickel chloride was applied percutaneously to the abdomen of three guinea pigs daily for one-half hour. On the first day there was a well-marked erythema. Within four days the reactions were intense. After seven days the applications were discontinued because of the severity of the local lesions and because the pigs had lost weight rapidly and appeared to be in a very toxic condition.

A microscopic section from a moderately advanced lesion was made and prepared with the standard hematoxylin eosin technic. The epidermis was acanthotic, with a thickened stratum corneum which was detached at several points. There was much cellular débris. Throughout the deeper layers of the epidermis there was both inter- and intracellular edema. There was moderate engorgement of the papillary blood vessels. The epidermis showed only a slight degree of perivascular small round cell infiltration. There were no eosinophiles, giant, plasma, or epithelioid cells.

It has been observed among nickel workers that blond individuals are more susceptible to nickel dermatitis than are brunets. In the series of eight pigs on which 10 per cent nickel chloride was used there were included two pure black, two pure brown, and two entirely white pigs. There was no difference in the appearance time or in the intensity of the eruption in any of these pigs. There was no indication that skin pigment in any way influenced the development of the lesions.

It has been frequently noted that heat intensifies the reaction of a skin sensitive to nickel. In two of the above series of pigs treated with 10 per cent nickel chloride, local heat was applied during the period of percutaneous applications. This in no way influenced the intensity of the reaction. However, since the above observation pertains to metallic nickel, and not nickel in solution, it would seem likely that excessive perspiration resulting from heat, and perhaps the taking of nickel into solution in the form of the chloride, would influence the reaction in the case of metallic nickel, but not with nickel in solution as in these experiments.

From Experiment 1, the following conclusions are drawn: (1) Nickel dermatitis is constantly produced in normal guinea pigs by percutaneous applications of solutions of nickel chloride. (2) The lesions produced were similar in every respect to what has been described clinically as nickel dermatitis. (3) The intensity and the speed of the reactions were in direct proportion to the concentration of the solution used. (4) Heat and skin pigmentation did not influence the reaction produced by nickel. (5) No eosinophilia occurred in the lesions. (6) A certain degree of skin resistance developed to the weaker dilutions of nickel.

Experiment 2. Two guinea pigs were sensitized to horse serum by injecting 0.5 c.c. of horse serum intraperitoneally. Subsequent daily *percutaneous* applications of 2 per cent nickel chloride produced a local

reaction entirely like that in the unsensitized pigs. It was concluded that a preexisting protein sensitivity did not influence the cutaneous reaction to nickel.

Subcutaneous injections of 0.1 c.c. of a 2 per cent solution of nickel chloride were given to two normal pigs every third day for 12 injections, and 0.2 c.c. of 2 per cent nickel chloride to a third pig. This last pig lost weight and died after the fourth injection. Autopsy revealed subcutaneous edema and hemorrhage at the site of the last injection. There were extensive necrosis and hemorrhage extending up over the thigh and over the peritoneal surface. In the first two pigs the reactions consisted of local edema and hyperemia. These pigs also lost weight and seemed toxic. In one the injections had to be stopped after the third inoculation because the animal had become sick. It died two days later of pneumonia. The other pig survived the 12 injections. Reinjection of nickel into previous injection sites did not produce an increased local reaction. Injections at a far point did not light up previous injection sites, nor were the later local reactions in any way different from the initial one. Five days after the twelfth injection, half-hour applications of 2 per cent nickel chloride were begun. No reaction appeared until the twentieth day when a definite erythematopapular eruption was noted, which lasted only three days, in spite of continuous percutaneous applications.

Intradermal injections of 0.1 c.c. of 2 per cent nickel chloride were given to two guinea pigs every third day for twelve injections. Characteristic local reactions occurred after each injection. Edema and hyperemia developed in twenty-four hours, followed by central necrosis and sloughing in forty-eight hours. Later injections made in site of previous injections, and in distant sites, did not produce a more intense reaction than the initial injection, and there was no flaring at old reaction sites. These pigs lost weight and became progressively more toxic. Within five days after the injections were stopped all evidence of toxicity disappeared and daily percutaneous applications of 2 per cent nickel chloride for one-half hour were started. One pig in spite of daily applications for thirty days showed no reaction. The second pig developed a mild reaction on the twenty-first day. This persisted for three days and gradually subsided, despite continued applications.

Sulzberger[7] working with experimental arsphenamine dermatitis in guinea pigs believed that he could produce sensitization by the intradermal method. Animals were given a single intradermal injection of 0.1 c.c. of 0.15 gm. of neoarsphenamine in 10 c.c. of water. After seven days a local reaction appeared and increased in intensity up until nineteen days. A second intradermal injection was given after thirty days, and a severe local reaction occurred. This reaction was interpreted as being a reaction of hypersensitivity.

Accordingly, five guinea pigs were given an initial intradermal injection of 0.4 c.c. of 2 per cent nickel chloride. A local reaction, as previously described, resulted. After twenty-eight days a second intradermal injection of 0.4 c.c. of 2 per cent nickel chloride was given at a different site. The reactions which resulted locally were similar to those produced by the first injection. There was no evidence that any degree of hypersensitivity had been produced.

Intraperitoneal injections of 2 per cent nickel chloride were given to two pigs. One pig which received 0.4 c.c. intraperitoneally became toxic and died after the first injection. The autopsy was negative. The second pig received seven injections of 0.2 c.c. every third day. Percutaneous applications of 2 per cent nickel chloride for one-half hour a day were begun five days after the last injection. A mild transient reaction appeared on the third day and persisted for four days. Another intraperitoneal injection was given after the abdomen had become clear, and on the following day, while continuing percutaneous applications, the lesion reappeared and lasted five days. In spite of continued percutaneous applications thereafter the abdomen remained clear.

After the abdominal lesions produced by 2 per cent nickel chloride percutaneously had subsided in the above group of six pigs (two pigs inoculated intraperitoneally with horse serum; one pig intraperitoneally, one pig subcutaneously, and two pigs intradermally with nickel), 10 per cent nickel chloride was applied percutaneously for one-half hour daily. The reactions which occurred were exactly like those produced in normal uninoculated guinea pigs by the percutaneous application of 10 per cent nickel chloride.

All the twelve guinea pigs which had had severe skin reactions to 10 per cent nickel chloride were given, after a rest interval of two weeks, a single intradermal injection of a 0.2 per cent nickel chloride at a distant site. None of the sites of previous old lesions flared up. There was no increase in intensity of the reactions in the areas of injection.

To these same twelve guinea pigs, in which reactions to percutaneous applications of 10 per cent nickel chloride had entirely healed, 20 per cent nickel chloride was applied percutaneously on the opposite previously untreated sites of the abdomens. The reactions which resulted were the same as those described in the previous experiment, in which 20 per cent nickel chloride was used percutaneously. There were no flare-ups at the sites of the previous abdominal lesions. As before, the pigs lost weight rapidly and became very toxic.

Finally, intracardiac injections of 0.2 c.c. of a 2 per cent solution of nickel chloride diluted five times with normal saline were given to one guinea pig from each of the previously mentioned groups; to four other pigs in which had been produced percutaneous reactions to nickel, and

to two normal control pigs. In each instance there were mild convulsions, similar to those encountered when a heavy metal is injected intravenously, but none died. There were no flare-ups at the sites of any of the previous lesions.

From Experiment 2, the following conclusions are drawn: (1) Preexisting protein sensitivity did not influence the nickel reaction. (2) Pigs previously treated with 2 per cent nickel intradermally, subcutaneously, and intraperitoneally were more resistant to the percutaneous reaction than were normal pigs. This was not true with 10 per cent nickel. The reaction with solutions stronger than 2 per cent seemed, in every instance, to be definitely irritative. (3) "Focal" reactions could not be produced by subcutaneous or intradermal injections of nickel. (4) Reaction of sensitivity could not be demonstrated.

DISCUSSION

So-called drug allergy appears, in the large majority of instances, to be an idiosynerasy, which may be defined as a physiologic reaction, either plus or minus, but usually plus. This is in direct contradistinction to allergy, which is a different reaction. An example of an idiosynerasy is sensitization to arsphenamine which occurs in a small percentage of individuals. Arsphenamine dermatitis has been produced in animals, notably by Milbradt[6] and by Sulzberger,[7] but the reports have been conflicting. The experimental evidence does not explain conclusively the exact nature of the reaction of sensitization that occurs.

Bismuth dermatitis, when it develops in the treatment of syphilis by the intramuscular use of bismuth, does not seem to be a true sensitization phenomenon. Patch tests have only occasionally been positive, and then only in the previously involved areas. The dermatitis often regresses spontaneously even with continuation of bismuth therapy. There may be some analogy to the similar findings obtained with the percutaneous applications of weak solutions of nickel in the above experiments.

Sensitization to contact chemical substances, as frequently occurs in industries, is likely to be found in a high percentage of individuals, especially if the contacts are frequent or extensive. Bloch's[8, 9] conception of the concentration of antigens is of the greatest importance in the interpretation of the production of sensitivity. He found that, although normal nonallergic individuals only occasionally became sensitive to primula, by a concentration of the antigen (repeated applications of primrose extract to the skin), he was able to overcome the individual constitutional factor and transform the idiosynerasy into a typical allergy. The allergy was limited to the specific antigen, and could be demonstrated not only in human beings but also in guinea pigs. Bloch's conclusions have been repeatedly verified in many forms of occupational dermatitis, for example the sensitization of surgeons to bichloride solution, of

anatomists to formaldehyde, of painters to turpentine, and possibly of nickel workers to nickel.

Sensitivity to chemical substances is even more easily developed when the exposed individual has the hyperirritable type of skin which develops multiple sensitivities on only occasional contacts. The authors have repeatedly seen cases of sensitization to nickel which would fall into this category, and these cases will be summarized in a later report. Steiner[10] was able to obtain positive patch tests to nickel in 50 per cent of patients with neurodermatitis.

With the exception of generally allergic and atopic individuals in which sensitivity to nickel has occurred, dermatitis due to nickel has seemingly been due to (1) its primary irritant action, and (2) the greater concentration of the drug to which industrial workers are exposed, with a possible resultant alteration of the individual constitutional factor. Goldman's two cases belong in both of these categories. Schittenhelm and Stockinger[11] stated that all workers who were constantly exposed to nickel salts developed nickel eczema. Jadassohn,[4] however, has drawn attention to the fact that although nickel eczema is common in large nickel factories, it is only occasionally observed in the small nickel shops where contact is casual. He was able to obtain a positive patch test in the uninvolved areas in only one case although he stated that a positive patch test was not uncommonly obtained in the previously involved sites.

Bloch[8] suggested that the allergy which developed might be due in part to some unknown hormonal influence, but Milbradt,[6] working on the influence of different hormones on the course of experimental nickel dermatitis, was unable to make any definite correlations.

SUMMARY

Experimental nickel dermatitis can be produced constantly in guinea pigs. The experiments indicate that this is an irritative phenomenon rather than one of specific hypersensitiveness. A certain degree of local skin resistance can be developed. The various factors which influence this reaction have been described.

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THE SEDIMENTATION RATE IN HAY FEVER*

Before and During the Seasonal Exacerbation

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DIAGNOSTIC value has been ascribed by various authorities to the determination of the sedimentation rate of the red blood cells in allergic diseases. If the test really serves as an indication in such cases, it should be significantly decisive and outstanding when applied to the blood of a large number of hay fever subjects, and especially so if those studied include young persons presenting few pathologic complications. The particular information obtainable from such a test should remain constant before, as well as during, the hay fever season, and may perhaps show variations consistent with expectations and reports that the allergic state induces a change from the normal. Should such a change be discovered, the next problem naturally to present itself is the question of the effects, if any, produced by the hyposensitization with pollen.

The purpose of this article is the presentation of a complete study of the sedimentation rate of the red blood cells in hay fever subjects before and during the hay fever season; the changes noted as a result of treatment, and the effects of the test on subjects in the season who have had no treatment.

PREVIOUS INVESTIGATIONS

Schulhof[1] used the Linzenmeyer method in a study of allergic persons and some of their relatives. In his report on 610 nonselected cases he stated that 115 patients, or 19 per cent, had a much slower sedimentation rate than that shown by healthy subjects. On further investigation of these 115 cases he found that 52 patients, or 46 per cent, had some form of allergic disease. Hence, he concluded that a pathologically slow rate is found almost constantly in patients with allergic conditions. He also drew the conclusion that in an allergic patient a rapid or even normal sedimentation rate is indicative of the presence of a more or less serious disease complication.

In a study of a series of 150 allergic patients in all of whom the diagnosis of an allergic condition was definitely established, Uffe[2] found only 14 patients with abnormally slow sedimentation rates, that is, 9.3 per cent of the total. Patients with hay fever predominated in

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TABLE I

PROTOCOL ON SEDIMENTATION RATE STUDIES IN 42 HAY FEVER SUBJECTS BEFORE AND DURING THE SEASON

NO.	NAME	AGE	SEX	TYPE OF HAY FEVER	CLASS AS TO THE DEGREE OF SENSITIVITY	DOSAGE REACHED IN TREATMENT†	SEDIMENTATION RATE*		COMPLICATIONS
							BEFORE SEASON	DURING SEASON	
1	S. F.	14	M.	R.	C.	1300 units optimal dosage	N.	N.	None
2	B. B.	40	M.	R.	B. C.	4000 units	S.	S.	None
3	N. D.	35	M.	R.	B.	1000 units	N.	N.	None
4	N. C.	38	M.	R.	B.	5000 units	N.	N.	None
5	H. G.	42	M.	R.	C.	5000 units	N.	N.	None
6	S. E.	20	M.	R.	B.	5000 units	N.	N.	None
7	J. L.	25	M.	R.	C.	2000 units	N.	N.	None
8	D. L.	15	M.	R.	C.	2000 units	N.	N.	None
9	H. M.	40	M.	R.	C.	3000 units	N.	N.	None
10	J. P.	30	M.	R.	B.	2000 units	N.	N.	None
11	Z. S.	45	M.	R.	C.	9000 units	N.	N.	None
12	E. S.	18	M.	R.	B. C.	2500 units	N.	N.	None
13	R. K.	45	F.	R.	D.	100 units	N.	N.	None
14	W. W.	33	M.	T. & R.	C. for both	T 5000 units R 4000 units	N.	N.	None
15	I. P.	37	F.	R.	D.	8000 units	N.	N.	None
16	V. L.	40	M.	R.	B.	2000 units	N.	N.	None
17	S. F.	43	M.	R.	D.	0.12 mg. total N	N.	N.	Asthma psoriasis
18	P. L.	35	M.	R.	C.	0.03 mg. total N	N.	N.	None
19	M. F.	17	M.	R.	C.	0.1 mg. total N	N. N.	N. N.	Asthma all year
20	J. L.	45	M.	R.	D.	0.16 mg. total N	N.	N.	
21	J. B.	40	M.	T. R.	D. C.	T 0.1 mg. total N R 0.1 mg. total N	N.	N.	None
22	T. Z.	40	M.	R.	C.	0.05 mg. total N	N.	N.	Summer asthma
23	I. S.	44	F.	T. R.	D. for both	R 0.1 mg. total N T 0.08 mg. total N	N.	N.	None

TABLE I—CONT'D

NO.	NAME	AGE	SEX	TYPE OF HAY FEVER	CLASS AS TO THE DEGREE OF SENSITIVITY	DOSAGE REACHED IN TREATMENT†	SEDIMENTATION RATE*		COMPLICATIONS
							BEFORE SEASON	DURING SEASON	
24	S. W.	19	M.	R.	C.	500 units optimal dosage	F. Mod. F.	N.	Polyarthritis Rheumatica acute exacerbation at time of fast rate
25	S. S.	47	F.	R.	B.	4000 units	F.	N.	Menstruation at time of moderate fast rate
26	Y. Z.	35	F.	R.	D.	0.1 mg. total N	F.	N.	Menstruation at time of fast rate
27	S. C.	30	M.	R.	C.	0.2 mg. total N	N.	N.	None
28	M. M.	35	M.	R.	C.	500 units	N.	N.	None
29	D. R.	35	M.	R.	B.	5000 units	N.	N.	None
30	E. S.	19	F.	R.	C.	1000 units	N.	N.	None
31	F. G.	19	F.	R.	C.	1000 opt.	N.	N.	None
32	S. B.	40	F.	R.	B. C.	0.05 mg. total N	F.	F.	Toxic goiter
33	S. G.	24	F.	R. & T.	T-B. R-C.	T 0.006 mg. total N R 0.01 mg. total N	N.	N.	None
34	S. K.	38	F.	R.	D.	0.16 mg. total N	F.	F.	Pelvic inflam. disease
35	M. C.	42	F.	R.	C.	4000 units	F.	F.	Pansinusitis
36	C. R.	40	F.	T. & R.	B. for both	1500 for both	F.	F.	Rt. ant. disease with pus
37	M. G.	19	F.	R.	D.	1500 units optimal	F.	F.	Left ant. and ethmoid diseases
38	G. G.	45	F.	R.	C.	3000 units	F.	F.	Undetermined
39	I. M.	30	F.	R.	D.	0.16 mg. total N	F.	F.	Pregnancy
40	A. T.	33	F.	R.	C.	4000 units	F.	F.	Pregnancy
41	A. C.	32	F.	R.	B. C.	5000 units	F.	F.	Pregnancy
42	M. K.	30	M.	R.	C.	0.06 mg. total N	N.	N.	

*Patients in this study have been divided in the following groups:

1. Slow—In which rate was not more than 2 mm. by the end of the first hour.
2. Normal—In which the rate was from 3 to 10 mm. by the end of the first hour.
3. Moderately fast—In which the rate was from 11 to 15 mm. by the end of the first hour.
4. Fast—In which the rate was 16 to 20 mm. by the end of the first hour.

†The term "units" used here expresses pollen extract as standardized according to protein nitrogen content, as per Cooke & Stull.[6] This system of treatment was followed at the German Polyclinic. At the Gouverneur Hospital the extracts used were those standardized according to total nitrogen content.

Note.—R. = Ragweed. T. = Timothy. N. = Normal. F. = Fast. S. = Slow.

the group with slow sedimentation and those with asthma in the groups showing a normal rate and a faster than normal rate. He came to the conclusion that a normal sedimentation rate in allergic patients is *not* indicative of the presence of a more or less serious pathologic complication. The number of patients under observation, however, comprised only 22 purely hay fever subjects, and no study similar to ours was made regarding differences, if any, before and during the season, or regarding a comparison of those receiving treatment for the condition with those having none.

Westcott and Spain,[3] in their studies, concluded that "the erythrocyte sedimentation rate in uncomplicated noninfective asthma, hay fever, or allergic nonseasonal coryza, falls within the accepted normal limits and particularly in hay fever, toward the low normal limit. It is, therefore, of little value as a test in purely allergic conditions." They also stated that in those cases where infection is present, the more acute the infection, the more rapid is the drop in rate. Their investigation was made only on 24 patients with hay fever, and without observation of the time, and without mention whether the subjects were treated or untreated.

THE PRESENT STUDY

In making use of the Cutler method[4] of the sedimentation rate of the red cells, our study was carried out on a total of 63 hay fever subjects. In 42 of this number, the tests were performed before, as well as during, the hay fever season and on 21 subjects when they came for treatment for the first time, and when they were suffering with decided hay fever symptoms. The latter group had received no treatment whatsoever in the form of hyposensitization by injections of pollen extracts before the onset of the season and at the time when the test was made. In the group as a whole, it can be stated that the sedimentation rate was normal throughout. It was found to be the same in these allergic persons as in any other group of normal persons on whom observations had been previously reported in the literature.[4]

Only in 11 hay fever subjects of the total 63, the rate was fast; in one, moderately fast, and in another it was slower. The causes, however, for such increased rates were easily determined, except in one case; other complicating conditions being present. In three of these eleven cases, the patients showed marked sinus disease of an acute nature. One was found to be suffering from pelvic inflammatory disease of an acute nature; another from toxic goiter. Three patients were pregnant, and one was menstruating at the time of examination. Still another was afflicted with polyarthritis rheumatica. In only one instance was the cause of the fast rate undetermined. In the one case in which the sedimentation rate was moderately fast, the patient was menstruating.

In our opinion, other than allergic conditions are responsible for an accelerated rate, based on the following facts: In two cases of the abnormal group a fast sedimentation rate was observed before the onset of the season and a normal rate during the season. It was definitely

TABLE II

SUMMARY OF THE RESULTS OF SEDIMENTATION RATE STUDIES ON HAY FEVER SUBJECTS PERFORMED BEFORE AND DURING SEASON

TOTAL NO.	NO. WITH NORMAL RATE	NO. WITH INCREASED RATE	NO. WITH SLOW RATE	AVERAGE NORMAL RATE BEFORE SEASON IN MM. AFTER 1 HR.	AVERAGE NORMAL RATE DURING SEASON, IN MM. AFTER 1 HR.	NO. IN WHOM INCREASED RATE WAS ACCOUNTED FOR	PERCENTAGE NORMAL
42	29	12	1	6.6	6.8	11	93.5

TABLE III

RESULTS OF SEDIMENTATION RATE ON A GROUP OF HAY FEVER SUBJECTS IN SEASON WITHOUT HAVING HAD TREATMENT

NO.	AGE	SEX	TYPE OF HAY FEVER	RATE IN MM. AFTER 1 HOUR	COMPLICATIONS
1	15	M.	R.	6.4	None
2	48	M.	R.	4.0	None
3	31	M.	R.	11.0	Alveolar abscess
4	25	M.	R.	12.0*	None
5	28	M.	R.	6.8	None
6	31	M.	R.	4.0	None
7	26	M.	R.	4.5	None
8	32	M.	R.	5.4	None
9	35	M.	R.	8.0	None
10	12	M.	R.	2.0	None
11	30	M.	R.	8.4	None
12	32	M.	R.	6.6	None
13	43	F.	R.	9.0	None
14	28	M.	R.	6.7	None
15	38	F.	R.	4.5	None
16	26	M.	R.	9.0	None
17	41	F.	R.	9.5	None
18	30	M.	R.	5.9	None
19	25	F.	R.	10.0	None

SUMMARY OF THE RESULTS IN THE ABOVE GROUP

TOTAL NO.	AVERAGE AGE	NO. MALES	NO. FEMALES	TYPE OF HAY FEVER	AVERAGE RATE OF SEDIMENTATION OF RED BLOOD CELLS AFTER 1 HOUR
19	32	15	4	R.	7.06 mm.

*Although relatively increased, it was found normal in two hours, i.e., 17.0 mm. after two hours.

established that at the time the rapid (first) rate had been determined, one patient had been undergoing an exacerbation of polyarthritis rheumatica, and the other had been menstruating. (Table I, Cases 24 and 26.)

Table I is a detailed record of the cases included in this study. All patients received adequate treatment. All were investigated in respect to the degree of sensitivity and their general physical condition. The investigation included a thorough physical examination, x-ray examination of the chest, sinuses and teeth, a thorough search for other than respiratory and upper respiratory infections, and also blood and urine findings.

Table II is a summary of the sedimentation rates observed in 42 hay fever subjects before and during the hay fever season. We would call attention to the fact that there was only one patient with a slow rate; 12 patients showed an accelerated rate, and in eleven of these the cause of acceleration was determined. The number of cases showing an abnormality being deducted from the total, there remained as high as 93.5 per cent of this entire group of patients with a normal rate. Also, the average normal sedimentation rate before the season was about the same as the average normal rate during the season.

Table III lists the results of the sedimentation test on 19 hay fever subjects presenting themselves for the first time at the clinic, who showed definite symptoms and had never had any treatment. In the summary we show that the average rate of sedimentation of the red blood cells after one hour for this group is 7.06 mm.

COMMENT

Our study revealed that in a group of 63 hay fever subjects only one showed a slow sedimentation rate. This is contrary to Schulhof's statement that a pathologically slow sedimentation rate is found almost constantly in patients with allergic conditions. Out of 42 hay fever subjects observed before and during the season there were 29 subjects with normal rates. These had no disease complication whatsoever; again in contradiction to the observations by Schulhof, who expressed the belief that a normal rate of sedimentation in allergic persons is indicative of the presence of a more or less serious pathologic complication. There were 12 patients showing increased sedimentation rates; and of these five, or less than 50 per cent, had serious disease complications. The remainder had physiologic complicating conditions, such as pregnancy or menstruation.

While Uffe found a slow sedimentation rate in 7 out of 22 hay fever patients, we can report only 2 out of a total of 61 hay fever subjects investigated, as showing such a rate.

The results of our study seem to agree with those of Westcott and Spain, in finding that a normal sedimentation rate is the rule in hay fever subjects. We add the singular observation that it also remains normal during the hay fever season and that treatment with pollen extracts produces no effect whatsoever on the rate.

We believe therefore that the sedimentation rate is of no diagnostic value in hay fever subjects and cannot be used as a test, for instance, to determine alteration, either a rise or fall, of the immunologic state of the hay fever patient.

CONCLUSION

The sedimentation rate of the red blood cells in patients with hay fever who present no other pathologic complications of a destructive nature remains normal before as well as during the hay fever season and whether they receive treatment or are without treatment.

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PERENNIAL HAY FEVER FROM LYCOPODIUM*

A Case Report

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LYCOPODIUM is known, to those who have practiced medicine for some years, as a dusting powder but not as an allergen judging from paucity of references in the literature. The only report is that of Peshkin of a druggist. Among the allergists of this city no one has observed any atopic reactions to it. It is a very fine powder of acrid taste, somewhat pungent odor, fluffy, combustible, burning slowly with yellow flame. It is used in fireworks, probably combined with metals that are color producing, and acts in prolonging color effects by its slow combustion.

Our local hairdressers and department stores recently have been calling their patrons' attention to a new powder for oily scalp. This powder contains lycopodium. Unless one is aware of the allergenic qualities of lycopodium it may be easily overlooked, or the producing agent suspected to be orris root. Those who have had much experience with use of lycopodium are probably familiar with the fact that it is obtained from spores of *Lycopodium clavatum*. It may be suspected when one considers the growing importance of the fungi and spores as a cause of hay fever.

Recently the following case came under the care of one of us. The patient was a married woman, forty years of age, with an allergic family and personal history. Five weeks before we saw her, she contracted what she believed to be rhinitis. It would not yield to ordinary remedies so she took a trip to Florida. While there her symptoms became worse. These consisted of itching and burning in the eyes and nose, lacrimation, sneezing, rhinorrhea, obstructed nasal breathing, and malaise. The mucous membranes were edematous and moist. Positive intracutaneous reactions were obtained to horse dander, goat hair, cattle hair, pyrethrum, wheat, *Streptococcus hemolyticus, Micrococcus catarrhalis, Type 1 pneumococci* and *Streptococcus viridans*. None of these reactors explained her difficulties; so house dust and the powder she had been using for oily scalp were tested by intracutaneous method. Very severe reactions were obtained to these extracts. The hair powder was blown into her nostrils and the symptoms were immediately produced. Following this a shampoo for the hair was prescribed. Her hats, furs, and other

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clothing containing powder were thoroughly renovated. A change of sleeping quarters was made. The symptoms disappeared entirely within thirty-six hours. Several weeks later the patient was in a skeptical mood. The powder was again introduced into the nose and all of the original symptoms of "hay fever" followed immediately. There can be no doubt as to the specificity of the agent.

In addition to this case of lycopodium rhinitis we know that two friends of this patient were afflicted in the same manner, and were not relieved until our patient informed them of her experience. They had been using the same hair powder.

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EARLY, ACTIVE, VIRUS IMMUNITY, WITH PARTICULAR REFERENCE TO VACCINIA IN NEWBORN INFANTS*

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THERE is consistent agreement among physicians who have assayed vaccination of newborn infants, that as a group they are difficult to inoculate successfully with vaccinia. The proportion so responding has varied quite widely in different places and at different times, but has been smaller uniformly by comparison with older infants and children, in whom primary vaccination may be close to 100 per cent successful. In the general report on vaccinations in France, Camus[1] states that for the year 1930 in Paris, 42,137 living births were recorded; of these newborn infants, 32,747 (78 per cent of the total) were given their primary vaccinations in the obstetrical departments of Parisian hospitals. The positive inoculations amounted to about 67 per cent. L. Isaac[2] reports that there were 1,041 babies born in one of the Iowa hospitals, between January 1, 1932, and May 7, 1933, of whom 808 were vaccinated, with 260 "takes," 32.2 per cent successful. "Multiple acupunctures were made through a drop of vaccine placed on the skin." Behm[3] in Berlin, in 1882, successfully vaccinated 25 (76 per cent) of 33 newborn infants, using undiluted, humanized lymph, carefully impregnating each of twelve cuts divided between the two arms. He convinced himself of the activity of the lymph by control inoculations. Palm[4] in Göttingen in 1900, vaccinated 58 newborn infants of whom 50 (86 per cent) were successful with the first attempt, employing four to six cuts. Mensching[5] in Hamburg in 1920 vaccinated 684 newborn infants between one and three days of age, of whom 484 (71 per cent) were primarily successful, and 200 (29 per cent) unsuccessful. He reported on inoculations in four skin cuts, each 5 mm. long, separated by 1 to 2 cm., with "strong vaccine lymph." Schlossmann and Herzberg-Kremmer[6] in Düsseldorf, in 1932, vaccinated 36 infants from eleven to sixty-three days of age, of whom 21 (58 per cent) were successful primarily, and 14 by two, three, or five inoculations at short intervals, one only remaining negative. They regularly used a lymph virus, whose titer was 1:20,000 to 1:30,000, and in a few instances 1:200,000. The inoculated skin cuts were two in number, each just 7 mm. in length. Jelinek[7] in Berlin, in 1933, successfully inoculated at the first attempt

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17 (77 per cent) of 22 infants, nine days to nine weeks old, and all of 8 (100 per cent) from nine weeks to six months, using lymph virus of a titer from 1:5,000 and 1:10,000.

These references show extremes of successful primary inoculations, 32.2 per cent and 86 per cent, and technic of vaccination varying from multiple acupuncture to twelve skin cuts divided between the two arms. Potency of virus and its refrigeration likewise appear as variables. Schlossmann and Herzberg-Kremmer employed a uniform technic (two cuts 7 mm. long) and two strengths of virus, maintaining that these factors must be constant in order that variations in immunity and "skin refractoriness" might be appraised.

If the newborn infant is resistant to vaccinia because of immunity of greater or less degree, one might expect to find antivirus antibodies in his blood. Likewise, there might be specific cellular or tissue immunity of some degree. Nonspecific resistance to virus infection will be considered separately. As vaccinia virus is not likely to pass the placental barrier, and as fetal antibody response is absent or insignificant, immunity[8] is doubtless passive in nature.

Many efforts to protect babies against smallpox by inducing vaccinia in their mothers before birth, have been attempted. On the whole, the results in establishing a clinical immunity to vaccine virus in this way have not been significant. Schlossmann and Herzberg-Kremmer's recent (December, 1932) study, was based upon a clinical comparison of results of inoculation with vaccinia virus of 36 newborn infants and their mothers, and a comparison of the antibodies in the maternal and newborn bloods, as obtained immediately postpartum from the uterus and the umbilical cord. The titer of the maternal and infant bloods was determined upon the skin of rabbits after the respective serum had been mixed with a known amount of active virus and incubated.

Their conclusions in part are as follows: Antibodies received from the mother inhibit successful inoculation in some newborn infants. Passive immunity cannot explain absence of a "take" in an infant whose mother "took," and her blood showed absence of antiviral antibodies. Of 36 newborn infants, 8 had no "takes" while their mothers "took," and 8 others "took" while their mothers failed to "take." The serum of 33 mothers at delivery had an antiviral titer for vaccine virus from 0 to 1:200. In pregnancy, antiviral antibodies can be found in the serum seven years after the last vaccination. The antiviral titer for vaccinia virus is equally high in maternal and newborn bloods. Therefore, these antibodies pass through the placenta without loss. A newborn infant can be successfully vaccinated in spite of an antivirus titer of 1:80 for vaccine virus; on the other hand, a newborn infant may fail to "take," in the absence of such antibodies. Antiviral antibodies disappear from the newborn infant's blood within three to five months. One newborn

infant had an antiviral titer of 1:20 fourteen days after successful vaccination; at five months his titer was 1:200. Revaccinated adults may show 1:800 to 1:1,600. Variability in duration of immunity is shown by successful revaccination in one woman four years after her last "take," and in another failure of revaccination seventeen years after her last "take."

From this work, immunity in newborn infants accounts for only a small part of their resistance to successful vaccination, whereas figures showing newborn resistance to be a definite reality, were given at the beginning of this report. Dreyfus-Sée[9] claims that there can exist in the infant a specific tissue resistance to vaccinia virus unaccompanied by humoral reaction.

There remains a factor of importance, probably more important than antiviral antibodies or specific tissue immunity. This is the resistance of young, growing tissues to noxious agents, a peculiarity of newborn infants during the first months following birth while there is visceral and cellular hyperactivity. Wadsworth and Hoppe[10] have shown experimentally that "Embryonic guinea pig cardiac muscle growing in cultures in vitro possesses the power of neutralizing, binding or destroying diphtheria toxin." Such neutralization takes place through the intervention of growing tissue. It was mentioned above that Mensching reported as successfully vaccinated 71 per cent of 684 newborn infants; of 82 premature infants, 63 per cent only were successful in his group. The tissues of premature infants thus are seen to be more resistant to vaccination than those of newborn infants at term; their tissues are certainly younger, and when they are thriving, their growth in length and in weight is more rapid.

It has already been indicated that potency of virus is a variable factor in different places where vaccination studies have been carried out. Also, it has been pointed out that vaccination technic has varied. In general, it has been suggested in the reports giving technic of vaccination that groups of newborn infants inoculated with considerable skin trauma, contain the greatest proportion of successful results.

In our study of vaccinations in newborn infants, we found that technic was exceedingly important. The pressure method (Leake[14]) was employed, the needle being placed tangentially to the skin so that the point broke the horny epidermis with each pressure. In the first 38 newborn infants 10 pressures without rubbing, producing very slight skin trauma were used, of these 12 (31.6 per cent) were successful; 27 newborn infants were inoculated by 20 needle pressures causing slight skin trauma; of this group 6 (22.2 per cent) were successful and 4 doubtful. In the next group comprising 39 newborn infants, moderate trauma was employed by using 30 needle pressures and quite pronounced rubbing with the flat or shank of the needle, so that the skin was more traumatized and well impregnated by the vaccine lymph; 14 (36 per

cent) of these were successful and 8 doubtful. In the next group of 57 newborn infants, marked trauma was caused after making 30 strong needle pressures and rubbing the virus back and forth in the site with very real skin damage, sufficient to be followed occasionally by a slight serous ooze; 43 (75.4 per cent) of this group took, and one remained doubtful. In the next group of 289 consecutive vaccinations of newborn infants, 260 (90 per cent) were successful. With all of them severe skin trauma was practiced; 30 pressures with a fine needle were made so vigorously that not only the point but frequently a centimeter or more of the flat of the needle broke the horny layer of the skin, which was then rubbed back and forth and in the same manner back and forth at right angles to the first strokes. By this procedure the vaccine lymph seemed to be rubbed into the traumatized epidermis, and the subcutaneous tissues also were traumatized so as to affect the skin capillaries. Regularly there appeared a serous ooze after completion of the inoculation.

Two of us carried out all the vaccinations. There were individual differences in the technic, one of us (M.M.N.) regularly practicing more rubbing of the virus into the skin than the other. The highest percentage of "takes" regularly followed the severest traumatization carried out.

In the first 377 newborn infants all of the virus (calf lymph 1 part, 50 per cent glycerin in normal saline 3 parts) was of the same lot number. It was furnished for this study by Dr. John F. Anderson, of the Squibb Biological Laboratories. Great care was observed to keep the virus refrigerated from the laboratory to the moment of use. The manufacturers shipped it in vacuum bottles to which a bit of dry ice had been added. The vacuum container was well insulated and boxed, special delivery mail placing it in our hands in about fifteen hours, when it was refrigerated at once, and from day to day the actual capil lary tubes to be used, were carried in a vacuum bottle, in a well-insulated package, into the nurseries for newborn infants in Gallinger Municipal Hospital. Maintaining the activity of the virus by this attention to its refrigeration was a factor, we believe, as well as the technic of vigorous inoculation in bringing about 90 per cent of "takes" in nearly 300 consecutive vaccinations of newborn infants. Topley[11] states that "It is perhaps a plausible guess, though certainly no more . . . that an essential element in virus infections is entry into and multiplication within particular susceptible cells, and that an adequate concentration of antibody in the neighbourhood of these cells protects them from the virus. . . ."

In three-fourths of our study the identical virus was employed, so that this factor was constant. In the remaining fourth, virus from the same laboratory seemed to be equally potent. All of the newborn

TABLE I

ACTIVE, ACQUIRED IMMUNITY

ESTABLISHED IN THE EARLY WEEKS OF LIFE IN 67 PER CENT

SERIAL	NUMBER OF NEWBORN INFANTS	FIRST VACCINATION		FIRST REVACCINATION		SECOND REVACCINATION		INDICATION OF IMMUNITY	
		AGES	RESULT	AGES	RESULT	AGES	RESULT		
378	1	8 hours	0	9 days	Scar 5 × 5 mm.	7 weeks	Pustule 15 × 15 mm.	Nonimmune	
408	1	13 hours	0	8 days	Scar 12 × 12 mm.	1 month	0		Immune
429	1	16 hours	0	8 days	Scar 8 × 7 mm.	5 weeks	0		Immune
446	1	28 hours	0	8 days	Scar 5 × 3 mm.	4 weeks	Two pustules 14 × 8 mm. 10 × 10 mm	Nonimmune	
485	1	50 hours	0	6 days	Scar 7 × 7 mm.	4 weeks	0		Immune
438	1	7 hours	Papule 8 × 6 mm. No induration	6 weeks	0				Immune
Totals	6		5 unsuccessful. 1 successful.		5 successful. 1 unsuccessful.			2–33% nonimmune	4–67% immune
398, 399, 411, 413, 433, 435, 455, 464, 468.	9	1¾ hours to 28 hours	0	6 days to 9 days	0	1 to 2 months	Pustules 15 × 12 mm. to 20 × 20 mm.	These are controls: same virus, same method, same time. All had takes.	

infants were inoculated in the first days of life, giving us another constant factor, in the resistance of young growing tissues to noxious agents. Variable factors were immunity of the newborn infants, humoral and cellular, and vaccination technic. When this last was vigorous, and the virus rubbed into susceptible cells with traumatization of the subjacent reticuloendothelial cells, successful inoculation maintained a fairly constant level of 90 per cent in a fair-sized group.

It is of interest to know the immunity response to vaccinia which resulted in these newborn infants. This was studied in a group of six newborn infants with 9 newborn infants as controls, to ascertain in what percentage and how soon active immunity appeared. (Table I.) In this group of six, vaccination was successful in one inoculated at seven hours of age; in 5, second inoculations at from six to nine days of age were successful. At from four to six weeks of age vigorous revaccination failed of success in 4 (67 per cent), but was successful in two, aged four and seven weeks respectively. All of the nine controls, negative on the day of birth, and again at from six to nine days of age, produced good pustules at their third inoculations at from one to two months of age. This entire group was revaccinated with the same virus, by the same technic, and the same vaccinator, at almost the same time. Jelinek revaccinated older infants, one to three months after primary success, and found 26 per cent nonimmune.

TABLE II

IMMUNITY TO VACCINIA FOUND IN 69.2 PER CENT OF BABIES THIRTEEN TO SIXTEEN MONTHS OLD, WHO HAD BEEN SUCCESSFULLY VACCINATED AT AN AVERAGE AGE OF TWENTY-FOUR HOURS

AGE WHEN FIRST VACCINATED	RESULT OF PRIMARY VACCINATION	AGE WHEN REVACCINATED	RESULT OF REVACCINATION	IMMUNITY
Minimum: 3½ hours.	All had successful "takes"	Minimum: 13 months.	Successful: 16.	Nonimmune: 30.8 per cent.
Maximum: 125 hours.		Maximum: 16 months.	Unsuccessful: 36.	Immune: 69.2 per cent.
Average age: 24 hours.	Successful	Average age: 14¼ months.	Total number: 52.	Immune: 69.2 per cent.

In a group of 52 successful primary vaccinations at an average age of twenty-four hours, vigorous revaccination at an average age of fourteen and one-quarter months, 36 (69.2 per cent) were found to be immune and 16 (30.8 per cent) nonimmune. (Table II.) Here also there were the same virus, technic, vaccinator, and almost the same day. As controls, 5 infants fifteen months of age whose primary vaccinations at birth were negative gave 100 per cent successful results on revaccination. Correlation between the size of the skin lesion and the resulting immunity could not be made out. A small "take" may be followed by protection against vigorous revaccination; or may fail to do

so. The same is true of large primary lesions. This appears to be in harmony with indications that not only the skin but other tissues participate in antiviral activity, the reticuloendothelial tissue in particular. Regional lymph node swellings are well known, and enlargement of the spleen may be found during vaccinia (Lereboullet[12]). Invasion of the blood stream by the virus, and its demonstration on the tonsil, within three days of inoculation, have been reported by Gins.[13] In inoculation by way of the skin as generally performed, no clinical immunity develops in the absence of a skin lesion.

In summary it may be said that a very real resistance to vaccinia in newborn infants has generally been found. The resistance of young growing tissue to certain infections and toxins may be important in accounting for this lack of successful inoculation. Congenital immunity appears to be of small significance, although antiviral antibodies have been found in the blood; they are probably derived from the mother and disappear after a few months of life. Other factors in explanation are potency of virus and technic of vaccination. Rubbing an active virus into susceptible cells with traumatization may result quite uniformly in 90 per cent of successes. Even so, 10 per cent of the newborn infants in our most successfully inoculated group of 289, resisted primary vaccination upon the first insertion. Active immunity may develop by four to six weeks of age, and is shown to be present in 69.2 per cent of 52 babies well over a year after successful vaccination at birth. No correlation between size of the skin lesion or "take" and resulting immunity could be made out.

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DISCUSSION

DR. LESLIE N. GAY, Baltimore, Md.—Dr. Donnally has presented to us a very interesting phase of the reaction of the skin of newborn infants. The failure of a vaccination "to take" has from time to time troubled every physician.

It has been experimentally demonstrated that immunity is conferred to the newborn rabbit by the vaccination of the mother; furthermore,

in smallpox-infected countries, pock-marked infants have been born from mothers who have had the disease during the child-bearing period; their immunity is permanent.

The potency of the vaccine has been frequently blamed for the failure of "takes," and justly so. Unless the material is carefully chosen, a titer of 1:100 might be found in commercially prepared vaccine, a very impotent material, when a titer of 1:50,000 is the usual requirement.

Dr. Donnally refers to the refractory state of the skin to vaccination with vaccinia virus. I do not believe that he personally agrees with this assumption. The lesion from the virus is not an allergic manifestation; an attenuated infection is produced, characterized by pustule formation. I do not believe one can, therefore, apply the term "refraction" to this type of reaction.

It is questionable in my opinion whether the skin ever shows a complete refractory state; although there are occasions when a subsequent reaction to an injection is much less than the primary test. Other phenomena enter into the problem to cause such a variation, which is irrelevant to the present discussion.

The technic described by Dr. Donnally is by far the safest and most satisfactory, not only because of the 90 per cent of "takes," but because of the elimination of tetanus and secondary infecting organisms.

In a series of fifty batches of commercial vaccine cultured in the laboratory of the Johns Hopkins Hospital, 40 per cent contained nonpathogenic organisms, but no tetanus. By traumatizing the corium, the possibility of implanting tetanus is quite improbable as demonstrated by Armstrong, of the U. S. Public Health Service in his work with rabbits. The chances of secondary infection are likewise greatly minimized.

DR. WARREN T. VAUGHAN, Richmond, Va.—Dr. Donnally's paper reminds us that we are equally interested in immunology as in allergy; that we do not know as yet whether there is a clear distinction between the two conditions.

Dr. Donnally has enumerated for us the various factors which might play a part in a successful "take," and I should like to discuss some of them. One, Dr. Gay touched on and that is the method of making the inoculation, the emphasis being on the desirability of avoiding drawing blood and washing away the virus. Zinnser found that in experiments on rabbits he obtained a much higher percentage of "takes" just by rubbing the virus into the skin than by the usual scratch method of inoculation. Wright found that with the intracutaneous method of application he obtained 70 per cent "takes" against 8 per cent by the incision method.

The importance of avoiding the drawing of blood, as Dr. Donnally has done in the method which he advocates, seems very great to me. I do not see why the intracutaneous method, as done by Wright, should not be the method of approach.

Another factor is, of course, the potency of the virus. During the war we had many soldiers who failed to have a "take" in this country, but when vaccinated in France with the French virus had good "takes." Dr. Donnally mentioned the difference in satisfactory "takes" recorded

by French observers and by American observers. In France they use more of the green virus that has not been kept in contact with glycerin for a long time, which definitely cuts down the infective activity of the virus.

Another factor is that of some difference in the infant or even the premature infant, that may play a part in his reacting differently.

It seems entirely possible to me that a child under a few weeks of age may be biologically different than older individuals.

DR. DONNALLY.—I had to leave out one paragraph and will take this opportunity to put it in. There is no immunity in the ordinary method of vaccination into the skin unless we get a skin lesion. That is well established and I had controls, which likewise established that well-known fact. Then there are other tissues than the skin, apparently, that participate in the production of immunity; the reticuloendothelial system in particular, and that, by the method I advocated, was traumatized when the virus was rubbed into the skin. We know that in vaccinia the lymph nodes enlarge; that occasionally the spleen may be found enlarged; and that virus has been recovered from the tonsil within three days of inoculation, and likewise from the blood stream.

FOOD ALLERGENS

III. The Leucopenic Index, Preliminary Report*

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In 1920 Widal, Abrami and Iancovesco[1] proposed a new test for liver function which they designated the hemoclastic crisis or colloidoclastic crisis test. The procedure consisted of the administration of 200 c.c. milk in the postabsorptive state. A positive reaction, indicative of hepatic dysfunction consisted in a falling curve of total leucocyte counts, falling blood pressure, and prolonged clotting time. Their studies indicated that the reaction could be correctly interpreted by following the white counts alone.

At the time that this test was proposed the general consensus of opinion was that the ingestion of food is followed by a digestive leucocytosis. A positive colloidoclastic reaction was manifested by a digestion leucopenia.

The authors' theoretical explanation was that, with the liver functionally damaged and unable to control adequately the passage of absorbed materials from the portal system into the general circulation, absorbed milk protein or partially digested milk protein passed through the liver thereby producing in mild degree the manifestations of protein shock. As is well known, anaphylactic shock is accompanied by leucopenia.

When this test was proposed, it was given thorough trial, and the conclusion of the majority[2] was that it was not a reliable test for liver function. While reaching this same conclusion, I did see many cases in which milk did cause a fall in total white count. Many of this group were subsequently found to be allergic to milk.

In April, 1932, a patient known to be allergic to milk, which in her case was responsible for attacks of migraine, drank a glass of milk for the first time in two years. Within three-quarters of an hour she was suffering from a very severe hemicrania, sufficient to require her going to bed in a darkened room, and which was accompanied by a very pronounced fall in the total white count, from the previously determined fasting level.

It occurred to me at that time that if a leucopenic response follows the ingestion of milk by one allergic thereto, and if this represents an

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allergic response rather than one due to hepatic insufficiency as had been maintained by Widal, Abrami and Iancovesco, it is probable that a similar response will follow the ingestion of other foods to which one is allergic. In this case a test method might be developed, to supplement the cutaneous test in the diagnosis of food allergy.

When next seen in August, 1933, the patient kindly consented to cooperate in a series of such food studies. Hers was an unusually appro-

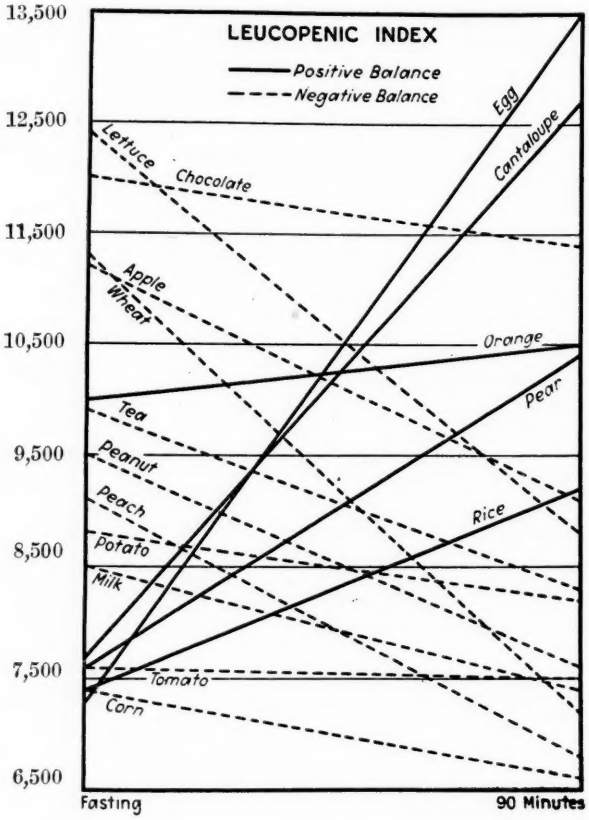

Chart 1.

priate case for trial, since she had carefully followed her diet from the allergic point of view for four years and knew very definitely what symptoms she could anticipate from the eating of different foods. She had in the past experienced quite a variety of symptoms from foods, especially migraine, urticaria, mucous colitis, vertigo, nausea, and a neuritic type of pain in the right arm.

Chart 1 indicates the leucocyte response following the ingestion of individual foods. Tests were done either after fasting overnight or in the early afternoon, five hours after the last preceding meal.

The patient knew that she could eat eggs, cantaloupe, orange, pear, and rice with impunity and, as shown in Chart 1, their ingestion was not followed by a leucopenic response.

She knew from previous experience that lettuce often caused abdominal pain. When she was tested with lettuce, the white count dropped over a period of ninety minutes from the previous fasting level, and she experienced generalized abdominal pains with urticaria. She knew that chocolate sometimes caused allergic symptoms. The white count fell slightly, but at the time of this test she experienced no symptoms from the eating thereof. The eating of apple was followed by leucopenia and a general toxic feeling which she described as being "droopy." Wheat produced hives; tea was followed by a mild headache and a droopy,

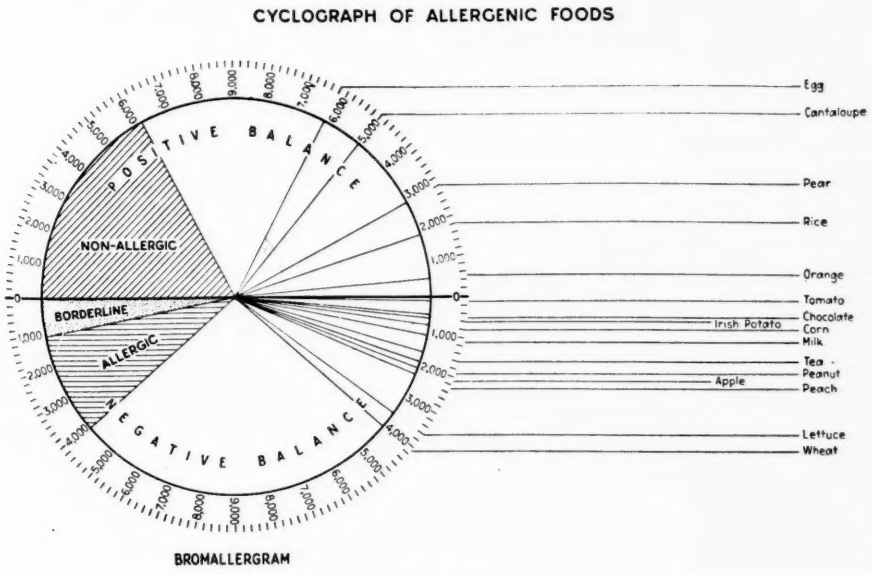

Chart 2.

loggy, no 'count feeling; peanuts caused an increase in urticaria; canned peaches produced a mild headache; Irish potato caused no symptoms, nor did milk on this occasion; tomato was followed by colonic pain; and the eating of corn was followed by a neuritic pain in the right shoulder, urticaria and vertigo.

Chart 2 presents the same information as shown in Chart 1 and represents an effort to present the curve in a more readily visualized form. With each food the fasting white count is reduced to zero and the postprandial count is corrected accordingly. For example, the fasting white count for eggs was 7,300; that taken ninety minutes after the ingestion of eggs, 13,500; 7,300 was subtracted from both of these figures. The starting point is thereby reduced to zero, but the angle of the curve remains the same. The fasting count for lettuce was 12,400; the post-

prandial count 8,800; 8,800 was subtracted from both. The difference is shown in Chart 2 by a drop below the base line.

Among the foods listed in Chart 2 as having a positive balance, none caused symptoms. Of the foods producing a negative balance only chocolate, Irish potato, milk and apple failed to produce symptoms. With the single exception of apple we may class these foods on the basis of the bromallergram or food-allergy-graph as follows.

Positive balance, no drop in white count; foods nonallergenic in this particular case.

Negative balance, with a sharp drop of more than one thousand; definitely allergenic.

Negative balance with a slight drop, less than one thousand; borderline. May or may not produce symptoms. The patient may be in a balanced allergic state in regard to these particular foods.

The correspondence in this first case was so striking as to suggest an actual relationship between the leucopenic response and allergic sensitization. Since last August we have made nearly three hundred leucopenic index studies on allergic individuals, using various foods. The results in this series will be subject for a later report. Briefly, we find a reasonably high correspondence between positive skin reactions and leucopenic responses. At the same time there are many in whom there is no correspondence, and quite a few in whom there is no correspondence with symptoms, certainly more such than we had hoped when we saw the startling correspondence in the case reported above. But this is equally true with regard to the ordinary skin tests, and probably no more so than with the skin tests.

Even though the skin tests may be reliable in only 50 per cent, as has been often stated, it is nevertheless a most helpful adjunct in the study of food allergy. Even if the leucopenic index should eventually show no higher efficiency, I have ample reason to believe that a combination of the two methods of study will still further increase our diagnostic effectiveness.

We have had patients who were skin test negative, both by scratch and intracutaneous methods, to certain foods but who showed positive leucopenic indices thereto and whom we were able to relieve only on the basis of the information gained from the leucopenic index studies.

The test as we are doing it today is applied as follows: The patient reports to the office in the morning in the fasting state. Two fasting white counts are made at ten-minute intervals. The patient then eats an average portion of the food to be tested. Subsequent white counts are made at fifteen-minute intervals for one hour. A final white count is made at the end of an hour and a half.

The same pipette and counting chamber are used for every reading on a given patient. A fluctuation of 2,000 in the total white count is allowed as normal. A drop of more than 1,000 below the mean of the two

fasting counts is regarded as of possible significance. The character of the entire curve is also considered in interpretation. Some reactions interpreted as positive will show a pronounced drop at some point during the curve. Others will show a general low range with no pronounced drop. Occasionally we have seen what we term a paradoxical curve in which there is a wide fluctuation, as much above as below the base line. We have as yet made no attempt to interpret these.

If the ingestion of an allergenic food is followed by leucopenia, it makes no difference whether a normal digestion leucocytosis does exist or not as has been recently maintained by Garrey and Butler[3] and by Raisky.[4] In other words we are not so interested in counts above the base line as in those below. It should be noted, however, that recent work by Lawrence, Stephens and Jones[5] indicates that a digestion leucocytosis of mild degree does actually exist.

The fact that the patient has been up and around for some time before reporting to the office, and remains in very much the same physical state throughout the test eliminates the factor of recumbency which has been emphasized by Garrey and Butler.

Our experience has been that fasting serial white counts do not fluctuate more than 2,000 as a rule, although we have observed one with a fluctuation in ten minutes of slightly over 3,000. Servantie, Panzat and Monod[6] found fasting serial fluctuations of from 2,000 to 3,700.

SUMMARY

A method is described for specific testing in food allergy based upon the presence of a specific digestion leucopenia following the ingestion of foods to which the individual is allergic.

The rationale of the method is discussed and the technic given in detail.

The results obtained in the first case so studied are discussed.

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REPORT ON INSULIN SENSITIVITY WITH ATTEMPT AT PASSIVE TRANSFER*

JOHN A. MURPHY, M.D., JOSEPH T. BEARDWOOD, M.D.,
AND MERLE M. MILLER, M.D.
PHILADELPHIA, PA.

ISOLATED reports of cases of insulin hypersensitivity have been published periodically for the past decade. The number of cases has varied widely in these observations. A range from less than 1 per cent to 15 per cent of cases treated with insulin can be found.

The severity of the reaction is most important. Some patients have only a local irritation, an area of edema and inflammation, while others manifest a generalized urticaria and angioneurotic edema, and those having other forms of allergy will often exhibit their particular allergic syndrome as a result of insulin therapy. We believe the percentage of local reactions is relatively high, and we have found two in 940 cases of marked general symptoms. These two cases are reported in more or less detail, with an attempt at passive transfer from one case.

A fairly comprehensive bibliography on this subject is found in the report of Allen and Scherer,[1] who recorded six cases of insulin allergy.

CASE REPORTS

CASE 1. Mrs. C. L. was admitted to the Graduate Hospital Feb. 2, 1934, in the Metabolic Department. A diagnosis of diabetes mellitus had been made four years earlier. Her ailment was under control with a dietary regime, but as she had lost 22 pounds in weight during the past three years, she was instructed to eat more. This resulted in sugar appearing in the urine, and she was hospitalized to secure a better maintenance diet.

She was in the hospital five weeks, and only one urine specimen showed sugar, after she had been without insulin for two days, and had had several five minim injections of adrenalin during the preceding four days.

The blood sugar was 148 mg. per cent on admission, and she was placed on an 1,800 calorie diet of 120 gm. carbohydrate, 60 gm. protein, and 120 gm. fat. On the fourth day, the blood sugar rose to 203 mg. per cent, but dropped to 146 mg. per cent the next day, rose to 169 mg. per cent on the sixth day and was 166 mg. per cent on the seventh day, when she received 4 units of insulin. The next, or eighth

*From the Graduate School of Medicine, University of Pennsylvania.
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day, the blood sugar was 222 mg. per cent, and 9 units of insulin were given. Insulin was gradually increased until she was getting 15 units daily, in two doses, which held the blood sugar under control.

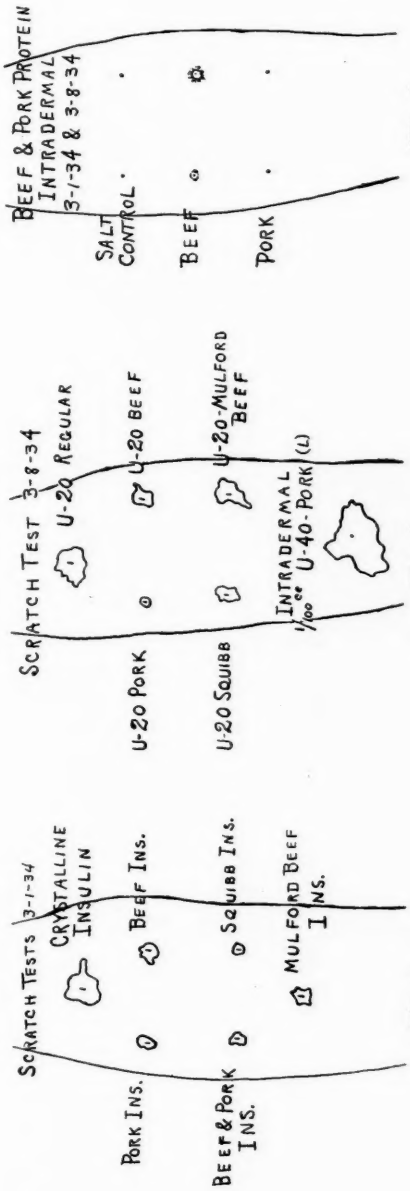

Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1, 2, and 3.—Patient C. L. Figs. 1 and 2 show insulin reactions.

The patient had had three or four doses of insulin three years previously. The first dose of insulin on this admission was given on Feb. 9, and she received it daily thereafter. She developed her first reaction on Feb. 16, seven days later, following the fourteenth injection.

The reaction was characterized by a generalized urticaria with marked itching at the site of injection. Lilly's regular insulin had been used up to this point. On Feb. 17, Lilly's special insulin (pork) was given for the morning dose. Two or three hours later she had another severe urticarial reaction. Mulford's beef insulin was substituted for the evening dose, and was followed by a more severe and a more generalized reaction. This reaction was augmented by four intradermal tests with Lilly's regular, Lilly's special, Mulford's and Squibb's insulin products, 0.05 c.c. of each, one hour after the evening meal. The reaction was ameliorated by the injection of 5 c.c. of a 20 per cent solution of sodium decholate.

She received her last injection of Lilly's special pork insulin the following morning and again had a reaction, but it was less severe than

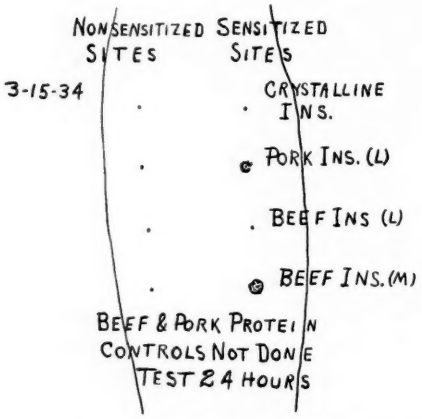

Fig. 4.—Transfer A, normal.

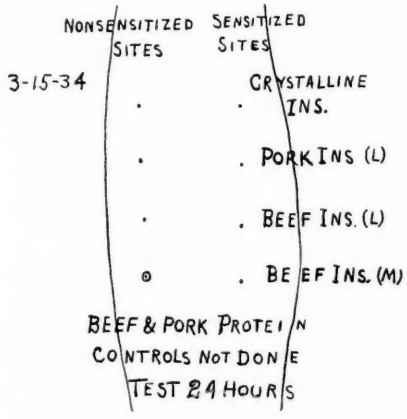

Fig. 5.—Transfer B, nondiabetic.

the one of the previous evening. Three days after stopping insulin the urticaria had entirely disappeared.

The patient was referred to the Allergy Department for study, where typical positive allergic reactions were obtained by the scratch technic to crystalline insulin, beef insulin, regular insulin (U-20 Lilly), and insulin, one of which was pure beef, from two other producers. There was no reaction by the scratch test to pork insulin. As a check on this product, we applied 0.01 c.c. of a U-40 pork insulin by the intradermal test and obtained a 6-plus reaction. All the test sites were itchy and the reactions persisted for forty minutes.

The illustrations represent the true size and contour of the skin reactions obtained.

Fig. 1 shows typical allergic reactions by the dermal method to crystalline insulin and several lots of commercial insulin. The major reaction is to the crystalline product.

Fig. 2 is a retest of commercial insulin of different animal sources, and, like the first, indicates general insulin sensitivity with a less marked reaction to pork insulin. As a check, a stronger insulin from pork was tested intradermally and a prompt reaction occurred.

Fig. 3 represents two intradermal tests on different dates with beef protein and pork protein, showing a moderate reaction to beef protein of the type often seen in testing with food proteins. The beef protein reaction and the negative result to the pork insulin scratch test (although positive intradermally), combined with the fact that the patient had no general reaction after the tests, led us to believe that a concentrated pork insulin could be used if necessary.

Fig. 4 gives the results of passive transfer to a normal subject. It shows some slight indication that transfer was accomplished, but this

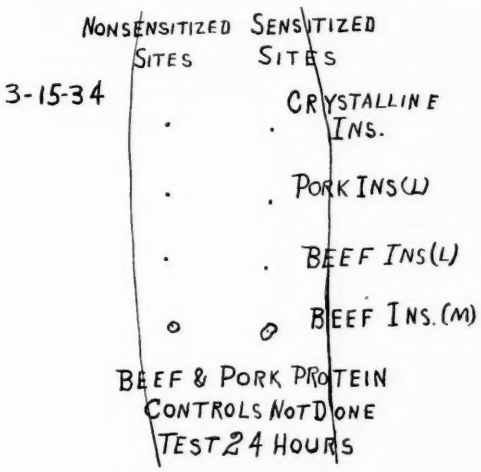

Fig. 6.—Transfer C, diabetic.

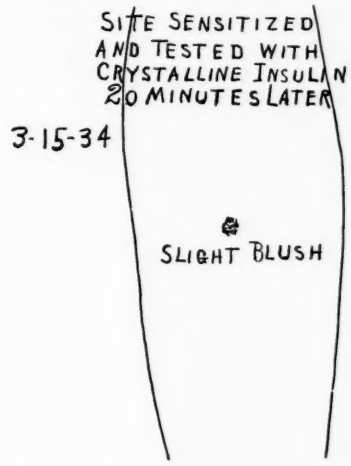

Fig. 7.—Transfer A, normal.

is questionable. Fig. 5, also on a nondiabetic subject, failed to show any evidence of transfer. Fig. 6 on a diabetic patient taking insulin regularly also failed to support the attempt at transfer. Fig. 7 represents a prompt test on a sensitized site and shows a slight erythema, but insufficient to indicate successful transfer.

CASE 2. Mrs. A. B. was admitted and her diet adjusted to 5-3-3 units of insulin. Seven days after starting insulin the course was interrupted for two days by an abdominal operation, was resumed the day after operation, and continued for four days, when a severe reaction characterized by marked dyspnea occurred. This first reaction was promptly controlled with a hypodermic injection of histamine hydrochloride. Similar reactions followed subsequent doses of insulin and failed to respond to histamine, and it was necessary to use adrenalin. A change from pork insulin to beef insulin was made with very satisfactory results.

The blood sugar varied from 79 mg. per cent to 212 mg. per cent and she was finally adjusted by a suitable diet and discharged.

Approximately three months later, during which time the diet was not followed, 8 units of insulin were recommended which promptly produced a very severe and alarming attack of asthma. The patient had formerly suffered with bronchial asthma and so was allergic. The insulin used was from pork.

She was skin tested on two occasions about a month apart and reacted to all brands of insulin by intradermal tests. She also reacted to pork protein but not to beef protein and placed on beef insulin she had no untoward reactions.

Figs. 8 and 9 represent the reactions to the several types of insulin and to beef and pork. These illustrations indicate some sensitivity to

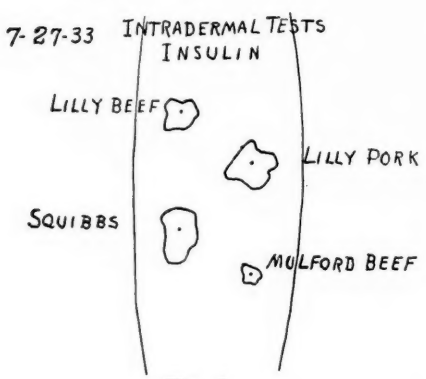

Fig. 8.

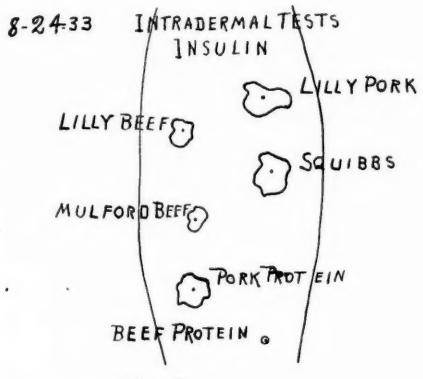

Fig. 9.

Figs. 8 and 9.—Patient A. B.

insulin, but not sufficient to cause any disturbance. When added to her rather marked pork protein sensitivity, however, her allergic balance was upset.

These two cases, similar in having reactions following an injection of insulin, both occurring about seven days after their primary dose, differ in that the major reaction in the first case was urticaria, and in the second was asthma. One patient was a known allergic, the other was not.

Both had had previous insulin injections. A change of the source of insulin helped one patient but not the other.

1803 PINE STREET

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THE INHERITANCE OF ALLERGY*

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Clyde E. Keeler, S.D.
Boston, Mass.

THE accompanying pedigree chart collected by one of us (C. S. B.) shows the occurrence of allergic manifestations among the members of five generations of a family represented by 236 males and 218 females or a total population of 454 individuals. Of these persons 50 males and 52 females, or a total of 102, have allergy. They exhibit asthma, eczema or hives, hay fever, migraine, gastrointestinal upsets, allergic rhinitis, and anaphylaxis, or several of these manifestations.

Of the affected members of the family 84 exhibit but a single manifestation of allergy, 13 bear two manifestations as shown in Table II. These classes are divided almost equally between males and females. No female bears more than two manifestations; whereas four males bear 3 each, and one male bears 4. In view of the small numbers we cannot say whether or not the absence of females in the latter two classes has any significance.

Table I

	MALES	FEMALES	TOTAL
Population represented	236	218	454
Persons having allergy	50	52	102

If we tabulate the number of persons bearing each type of allergy (Table III) we find that there are 50 persons having asthma, 44 having hives or eczema, 13 having hay fever, 8 having migraine, 6 having gastrointestinal disturbances, 2 having allergic rhinitis, and 2 having anaphylaxis. These types are almost equally distributed between males and females. In the only cases in which there might be suggested a difference in distribution due to sex (hay fever and gastrointestinal upsets), the figures are too low to be of statistical significance.

Table II

NUMBER OF EXPRESSIONS MANIFESTED	MALES	FEMALES	TOTAL
1	39	45	84
2	6	7	13
3	4	0	4
4	1	0	1

*From the Bucher Clinic, Champaign, Ill., and Howe Laboratory, Harvard Medical School.

TABLE III

EXPRESSION EXHIBITED	MALES	FEMALES	TOTAL
Asthma	24	26	50
Eczema-hives	22	22	44
Hay fever	9	4	13
Migraine	3	5	8
Gastrointestinal disturbances	5	1	6
Rhinitis	1	1	2
Anaphylaxis	2	0	2

If we group all persons showing particular combinations of two manifestations (Table IV), we find a suggestion that more males than females are severely affected; but, when we classify those having 3 manifestations, we find that part of this apparent deviation from equality is due to the presence of the 4 males in Table V, which have been necessarily recorded under two headings in Table IV (under asthma with hay fever and also under hay fever with hives, also asthma with hives). One male alone suffers from gastrointestinal upsets with hives or eczema plus allergic rhinitis with anaphylaxis. When we examine the pedigree, we note that the incidence of allergy is much too high for the character to be due to one or more pairs of recessive factors in the abscence of inbreeding. A study of the pedigree chart reveals that the tendency to transmission is quite definite and must be due to a single dominant gene substitution.

TABLE IV

COMBINATION OF TWO EXPRESSIONS	MALES	FEMALES	TOTAL
Asthma + eczema-hives	0	5	5
Hay fever + eczema-hives	5	0	5
Asthma + hay fever	4	0	4
Gastrointestinal disturbances + migraine	2	0	2
Gastrointestinal disturbances + eczema-hives	2	0	2
Eczema-hives + migraine	0	1	1
Rhinitis + migraine	0	1	1

TABLE V

COMBINATION OF THREE EXPRESSIONS	MALES	FEMALES	TOTAL
Asthma + hay fever + eczema-hives	4	0	4

If we classify the matings according to the type of the parents, we find that there are five matings of allergic times allergic. These matings produced 5 allergic males, 7 allergic females, 6 nonallergic males and 3 nonallergic females, or a total of 12 allergic persons to 9 nonallergic persons. Upon the basis of a dominant unit-character, we here expect 15.75 allergics among a progeny of this size. Hence, although the numbers are not large enough to be significant, the indications are that the allergic class is actually deficient.

There are 16 matings in which the father was allergic and the mother nonallergic. These produced 12 allergic males, 12 allergic females, 24 nonallergic males and 18 nonallergic females, or a total

TABLE VI

COMBINATION OF FOUR EXPRESSIONS	MALES	FEMALES	TOTAL
Gastrointestinal disturbances + eczema-hives + rhinitis + anaphylaxis	1	0	1

of 24 allergic individuals to 42 nonallergic individuals. Here we find a deviation of 9 from the expected equality, due to deficiency of the allergic class.

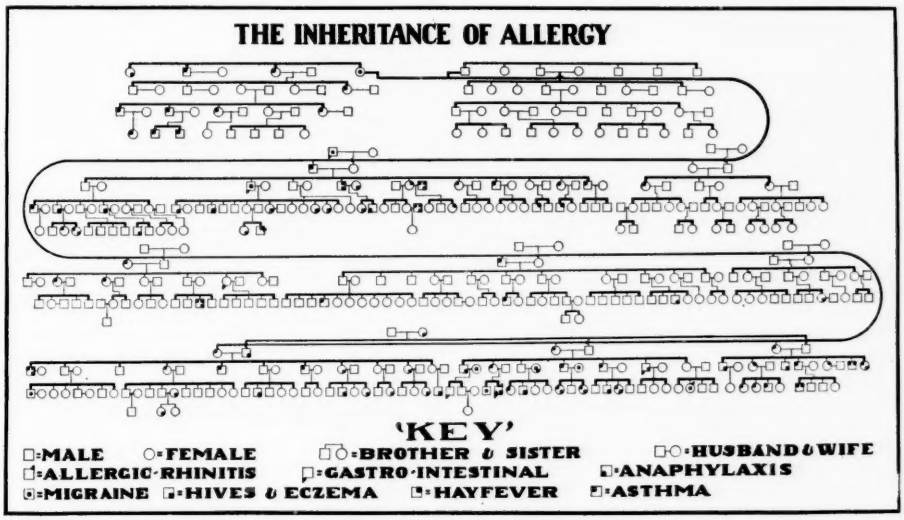
THE INHERITANCE OF ALLERGY
'KEY'
□=MALE ○=FEMALE □○=BROTHER & SISTER □○=HUSBAND & WIFE
□=ALLERGIC-RHINITIS □=GASTRO-INTESTINAL □=ANAPHYLAXIS
□=MIGRAINE □=HIVES & ECZEMA □=HAYFEVER □=ASTHMA

Chart 1.

There are 20 matings of allergic females times nonallergic males which produced a total of 16 allergic males, 13 allergic females, 27 nonallergic males and 27 nonallergic females, or a total of 29 allergic persons to 52 nonallergic persons. This is a deviation of 12.5 from equality. If we combine this progeny with the previous progeny, we find a total of 53 allergic individuals to 96 nonallergic individuals. The percentage of allergics is 35.5. The deviation from the expected equality is 21.5, which is probably of statistical significance because it is more than 5 times its probable error of 4.12. This indicates that there is a significant deficiency in the expected allergic class which may possibly appear as normal overlaps, or individuals who bear and transmit the allergic gene but in whom the character is not expressed because of other factors.

If this is true, we may expect to find about the same ratio of allergic to nonallergic persons among the progeny of nonallergic parents (one

of whom is a normal overlap) who produce some allergic young and who had an affected parent. There are 13 such matings in which a suspected normal overlap has produced some allergic young. The progeny of these matings consist of 12 allergic males, 6 allergic females, 16 nonallergic males, and 14 nonallergic females. This is a total of 18 allergic and 30 nonallergic individuals. The percentage of allergics is 37.5, which is quite similar to the percentage of allergic individuals found for progeny of the allergic times nonallergic matings, namely 35.5. Hence, it is evident that normal overlaps times nonallergic persons produce the same ratio of allergic to nonallergic persons as are produced by allergic persons times nonallergic persons.

A further examination of the pedigree reveals that there is a tendency for certain phenotypes of allergia to become segregated in certain subfamilies; for example line 3, individuals 1, 3, 5, 9, and line 4, individuals 1, 2, 3, all inherited asthma; also line 8, individuals 13, 16, 21, 25, 26, and line 9, individual 14, all inherited hives or eczema, which may be due to similarity of residual hereditary background within these particular families.

In recapitulation, we may say that this family transmits allergia as a simple dominant unit-character affecting in equal numbers both males and females. There is about a 12.5 per cent deficiency of the allergic classes due to normal overlaps. Among the allergic individuals the most common manifestations are asthma (in 49 per cent) and hives or eczema (in 42.1 per cent); whereas 17.6 per cent of the affected persons exhibit more than one manifestation of allergia.

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

TENTH ANNUAL MEETING, ATLANTIC CITY, N. J., APRIL 28, 1934

(CONTINUED)

A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of From Two to Ten Years.* ARTHUR I. FINK AND LESLIE N. GAY, BALTIMORE, MD. (Abstract.)

The literature concerning the etiology of urticaria is confusing because of the unreliability of skin tests and elimination diets in diagnosis, and the failure to follow patients over a sufficient length of time to determine the ultimate result. Hopkins and Kesten, for example, in a recent paper were unable to reach any definite conclusion as to the cause of the urticaria in 193 of 214 cases.

This series of cases has been followed from two to ten years, and an accurate follow-up report has been made within the past two months.

Of the 170 cases, 69 per cent were female and 31 per cent male. The usual age was the fourth decade, and the average duration of urticaria before consultation was four years. About 15 per cent of these patients had an allergic personal history; although 28 per cent had a positive family history of allergic conditions.

The eosinophile count averaged 1.2 per cent in 54 determinations. Of the entire group 27 per cent gave negative results to skin tests, and the significance of most of the positive tests was problematical.

The blood pressure in 57 patients was subnormal in 37 per cent and elevated in 15 per cent. Forty-eight per cent of 60 patients were underweight and 15 per cent overweight, and 68 per cent of 31 patients had a low gastric acidity while 13 per cent had a hyperacidity.

The patients were classified in the following etiologic groups: (1) Urticaria associated with foci of infection which embraced 30 per cent or 62 of the cases. Thirty-five patients underwent operation for removal of foci of infection; 74 per cent are reported cured. (2) The allergic group, comprising 20 per cent of the patients, and of these 75 per cent were symptomatically cured by avoiding the specific allergens; (3) the psychogenic group, with 18 per cent of the cases; (4) the endocrine group, comprising 5 per cent, associated with men-

*From the Protein Clinic of the Medical Department of the Johns Hopkins Hospital.

struation, pregnancy, menopause and hypothyroidism; (5) the undetermined group, comprising 25 per cent.

SUMMARY

One hundred and seventy cases of urticaria and angioneurotic edema studied from two to ten years are reported. Information on the progress of each patient has been obtained during the past two months.

Fifty-two cases were associated with infections; of these 74 per cent were permanently relieved by removal of the infected tissue.

Thirty-five cases were due to allergic factors; avoidance of the specific cause permanently relieved these patients of their urticaria.

Treatment of the psychogenic group was less satisfactory. It is our belief that the psychiatrist is far more helpful to these patients than the allergist.

The group of patients with disturbance of endocrine function responded satisfactorily depending on nature's physiologic adjustment; or on small doses of thyroid extract.

We have little to suggest concerning cause or treatment of the "undetermined group"; with further study the number will undoubtedly be reduced.

The average duration of symptoms in the entire group before consultation was about four years; the average period of observation since consultation was 3.7 years.

In conclusion, it is our belief that a more optimistic prognosis can be entertained provided a more careful diagnostic study of each patient is made with less emphasis on the importance of allergy per se.

DISCUSSION

Dr. Albert Vander Veer, New York City.—It seems to me that this is a very good paper to hear at this time. Most of us are rather discouraged with the treatment of urticaria.

When a patient with urticaria comes to the office, we proceed to look him over for a chronic infection; and if we can find infected tonsils, sinuses or teeth, or an appendix or gallbladder, we are pleased. We can send him away to have these attended to, which will take several months, and there is always the chance that he may never come back. If this last measure does not work, we have a sinking feeling in the pit of the stomach and have to get down to business.

We then take a very careful history and ask the patient to write out the things that he cannot take. If he is at all enthusiastic, he will draw up a list which makes *Anthony Adverse* look like an introductory chapter. We try to go through it and then give it up in despair. Then we go ahead with tests, using intradermal and scratch, patch and passive transfers, and everything else we can think of, or that has been suggested.

When the smoke of battle clears away, I think most of us will agree that this paper is very nearly correct in the results. A good many cases, probably the majority, will be found due to chronic infection, and if

this can be successfully treated, they clear up and stay clear. In the food cases, if you can get a good history you can often do something with them.

The most brilliant result that I can ever remember achieving was in the case of a girl who had eaten lobster and woke up covered with hives. I gave her adrenalin and ephedrine and told her to come in the next week, which she did, feeling practically well. I tested her out and with extreme conservativeness used a lobster extract dilution 1:1,000. It gave no immediate reaction, but the next day she proceeded to go through the same attack of urticaria which she had had before. She came back a week later and said that if it was all right with me she just would not eat any more lobster for a time—I said that I agreed with this and she went away. That happened eight months or a year ago, and I have not seen her since, but I am afraid that she is likely to walk into the office any time saying that she has eaten no lobster but still has the hives.

I should like to make one or two suggestions. I am not quite keen about the psychogenic group. I have a feeling that in the psychogenic cases there is some underlying cause that we ought to find out.

Then there are one or two foods which Dr. Fink did not mention. I think we find the most frequent are milk, chocolate and shellfish, more even than those he has mentioned, and among the drugs, I should like to add aspirin and luminal.

In conclusion I should like to thank Dr. Fink and Dr. Gay very much for a good paper. We needed it and it will give us a little more confidence to go on with these cases.

Dr. Francis M. Rackemann, Boston.—I have had one or two cases in which drugs were very important and the particular one was phenolphthalein. I find that a good many patients with chronic urticaria existing over a long period of time, have also chronic constipation, and I find they have been taking one drug or another for a long period of time. It may be phenolphthalein, or alophen, and I had a patient the other day who was taking A. S. & B. (aloin, strychnine, and belladonna), a pill. The patient had been taking this pill every night for something like five years, and she had urticaria, and thus far (it is only a few weeks, of course) she is better without that pill. Whether she will stay so, I do not know.

Dr. Marion B. Sulzberger, New York City.—Unfortunately, I see a great many cases of urticaria, and I should like to preface my remarks by saying that I do not find the cause of most of them and that I am unable to cure many of the chronic cases.

Concerning the psychogenic urticarias, as Dr. Vander Veer brought out, the question is: when are we justified in saying an urticaria is psychogenic? This is a difficult decision to make. All we can say is that there seems to be a psychic factor involved in some cases of chronic urticaria. But this is true in most diseases; certainly in asthma and hay fever, and perhaps even in such clearly infectious conditions as tuberculosis. It seems safer not to be too easily satisfied with the "psychogenic diagnosis" but to remember that the search for other causes is beset with great difficulties, and even the best testing may be hopelessly inadequate. In considering other causes, I should like to

stress what Dr. Rackemann said, namely that the list of substances must be materially lengthened.

I have seen several cases of urticaria from phenolphthalein, some from iodides, even in the form of iodized salt, and so forth. I think the investigation of the respiratory absorption of substances as possible cause of urticaria may be of greater importance than previously supposed. We know from the experiments of Dr. Milton Cohen, for instance, and from those recently performed by Dr. Vaughan and myself, that inhaled allergen can get into the blood stream, and does get in in sufficient quantity to cause urticarias. We must therefore scrutinize inhalant substances with the same attention and care which we now exercise in studying foods as possible causes of urticaria. I think that microorganisms, such as fungi (monilia, etc.) have not yet been sufficiently studied in urticarias. All in all, I should say that allergen-free rooms, elimination diets, and consideration of saprophytic and pathogenic organisms must be much more exhaustively employed in each case before we feel compelled to place it under the emblem of allergic defeat—"psychogenic."

Dr. Louis Tuft, Philadelphia.—I should like to ask Dr. Fink whether in any of the cases in the infective group he could make out a clear-cut relationship between an exacerbation of one of the foci and an outbreak of urticaria. I have never been quite satisfied that there was a relationship between focal infection and urticaria, and I wonder whether the clearing up of these foci, such as, for example, tonsillectomy, might not act in a nonspecific way very much as bacterial vaccine or autohemotherapy might do.

Dr. Milton B. Cohen, Cleveland.—It has been very gratifying to me to hear this paper of Dr. Gay and Dr. Fink, because they are so much more hopeful about the urticarias than our experience has led us to be.

We ought to differentiate them clinically into two groups: primary urticaria, the kind that springs up de novo in a patient who has no other kind of allergy. This is the kind with which you get nowhere; and the other type is the simple one that has urticaria complicating other allergies, in which you get fairly good results.

My experience has been that if you follow the cases of primary urticaria carefully and are successful in working them out, you will find the majority are due to drugs.

We have found frequently that in a case which we thought belonged in the infections group, in which there was a flare-up of a focus, if we quizzed the patient, we found that there was a flare-up of a focus and took the remedy for the flare-up, and then got urticaria. If you are not careful in such a case, you will attribute it to the infection when actually the cause is drug.

Aspirin is a common drug that causes trouble, and not only that, but these hundreds of things that are advertised—the pink colored solutions to wash your mouth and brush your teeth—these are all phenolphthalein solutions. We all contact with them. In studying a patient we give him a list of the things he may put in his mouth, so that when we put him on elimination, we know what is eliminated.

A fair percentage of hives will clear up if you follow that recommendation, and, if you do not, you do not find the cause of the hives.

We never skin test primary hives any more because we never learn anything by it. The food cases are found by dietary experimentation.

DR. FERNAND VISTZREICH, New York City.—May I ask a brief question: Did Dr. Gay come across cases of dermographic urticaria and what was his experience?

DR. GRAFTON TYLER BROWN, Washington, D. C.—First of all, I want to add my commendation of the excellent way in which Drs. Fink and Gay have handled this complex and difficult problem.

The high percentage (some 68 per cent) of patients in their series with a low gastric acidity, is worthy of note. This is quite an important factor, possibly more so in angioneurotic edema than in simple urticaria. Gastric analyses on patients with urticaria or angioneurotic edema, frequently reveal hypochlorhydria, achlorhydria, and at times complete achylia; and in many of these cases, sufficient doses of hydrochloric acid are all that is needed to clear up the trouble.

I might mention one case to illustrate this. A women seventy-two years of age was referred to me not long ago with severe urticaria, with which she had suffered constantly for three years. During this period she had been skin tested repeatedly by different physicians, and had reacted on intradermal tests to a large number of foods and other substances. There were so many of these supposedly allergenic foods, that she had been on almost a starvation diet, but in spite of this, the urticaria persisted. Blood tests showed a pernicious anemia, and a test meal revealed an achylia. Administration of hydrochloric acid with each meal cleared up the hives almost immediately, and she is now on a full diet.

Most of the urticarias that I see, unless they are associated with other allergic conditions, are apparently bacterial in origin. Urticaria in conjunction with asthma, hay fever, or eczema is almost always due to sensitization to one or more foods, and occasionally to inhalants. Where an individual has urticaria, however, with an otherwise negative personal history of allergy, the hives are usually bacterial or metabolic in origin.

In considering possible foci of infection, the intestinal tract is probably most often overlooked. Extraction of all infected teeth is important, but no more so than careful culturing of the stools. When the stool shows large numbers of *Streptococcus hemolyticus* or *viridans,* or *Staphylococcus aureus,* the urticaria can usually be cleared up with autogenous vaccine injections, combined with changing the intestinal flora by the use of sodium ricinoleate followed with acidophilus therapy.

Under the endocrine type, hypothyroidism is much more common than hyperthyroidism, and normalizing the metabolism will frequently relieve the urticaria. The hypothyroid cases usually respond to desiccated thyroid. One patient of mine with hyperthyroidism, chronic urticaria, and epileptic attacks, was definitely relieved by x-ray treatments, and apparently cured by partial thyroidectomy.

With reference to drugs as the cause of urticaria, I should like to mention quinine and ipecac. Although drugs seldom give positive skin reactions, I can recall two patients, one with hives from quinine and the other whose hives were caused by ipecac in cough medicine, who gave definitely positive "scratch" tests with these drugs.

Under inhalants, I have seen urticaria due solely to sensitization to

grass pollen, and also to orris root, without any hay fever or other respiratory symptoms.

Calcium medication supplemented with desiccated parathyroid and vitamin D in some form, has been all that was needed for some patients with urticaria or angioneurotic edema and a blood calcium deficiency.

Panteric tablets or capsules, or injections of autogenous blood, urinary proteose, or concentrated peptone extract have proved of great value in certain cases of urticaria.

DR. JOHN A. MURPHY, Philadelphia.—There is too much meat in this excellent paper to give a broad discussion of it; therefore, I shall select the psychogenic classification and simply report one case that I feel free to talk about because it happens to fit Dr. Vander Veer's classification.

This patient had chronic urticaria and angioneurotic edema for a period of three years, the attacks coming on once or twice a week and lasting from twenty-four to forty-eight hours, relieved by adrenalin. She noted that every time she got rather fatigued, the attacks would come on; but, after doing as Dr. Vander Veer and others have done, testing, and talking, and testing, and talking, I finally discovered that this lady had a domestic problem.

I prevailed upon her to select some friend in whom she had confidence, and unburden her soul. She and her husband were having some little difficulties. Before I had given her this advice, I had put her on 3¾ grains of decholin. Decholin is supposed to be a great choleric, flushes out the liver, and does a spring housecleaning job. Coincident with putting her on the decholin, she had, the second day after that, the severest attack of urticaria and angioneurotic edema she had ever had. This attack cleared up in forty-eight hours, and she has not had another attack for the past eight weeks.

Her urticaria began with her first knowledge of her domestic problem, which she kept as a personal secret for three years. I believe, in this case, the psychogenic factor was very definite because when this patient unburdened her mind, and confided in her father, arrangements were made for an adjustment that apparently was going to be satisfactory to all concerned. Then the attacks stopped. I am quite sure there are many factors we do not understand, and the different excitants we talk about are triggers. I believe her trigger mechanism was mental worry over her domestic situation.

DR. T. D. CUNNINGHAM, Denver.—I want to call your attention to an observation made several years ago, reported in the *Quarterly Journal of Medicine*, about the incidence of spasmophilia and the various reactions due to diminution in the blood calcium. That occurs at its height in January, February, or March. There apparently is the same incidence in the occurrence of urticaria.

This raises the question as to whether vitamins, blood calcium, and such things, do not have a great deal to do with urticaria. With this in mind, I have put the patients on a high vitamin diet during the time of the year when vitamins and sunshine are particularly scarce. If you prescribe a dose of calomel and salts, these measures will take care of almost as high a percentage as getting rid of the focus of infection.

DR. GEORGE L. WALDBOTT, Detroit.—Last year in early spring I had an unusually large number of patients with urticaria. Some of these

patients had nasal catarrhs which were due to tree pollen, and I believe that this epidemic of urticaria may have been caused by the tree pollen.

Another point is in line with what Dr. Cohen brought out in connection with urticaria in atopic and nonatopic patients. By an injection of horse serum, for instance, we can produce generalized urticaria in a sensitized individual if the dose is in excess of the amount which the patient can tolerate. This urticaria is allergic or anaphylactic. On the other hand, in a *nonallergic* person we may produce urticaria by an injection of horse serum under certain conditions, which is a part of the symptom-complex of serum sickness. I believe the nature and significance of both types of urticaria are entirely different.

DR. GAY.—I shall reply for Dr. Fink.

Dr. Vander Veer mentions in his discussion the psychogenic group, and this particular group has been of interest to a number of investigators. It is our opinion, as we have tried to emphasize in this paper, that urticaria is not a disease for the dermatologists. It is a disease that requires more than the external study of the skin, and psychogenic disturbance influences a large number of these individuals. In the particular group which we are reporting, consultation and advice have been given to us by the staff of the Henry Phipps Psychiatric Clinic. Frank discussion of the problems of life with individual patients, who fall into this group, has been of great help, giving a particular individual an outlet for discussion of his troubles, and even though relief of urticaria has been transient, it has proved our point.

Dr. Murphy refers to the psychogenic factor in individuals who are pregnant. It is our belief that psychogenic disturbance is not the cause of urticaria in pregnant women. Physiologic changes, which are initiated by pregnancy, we believe, are far more important in the production of the skin manifestation.

With regard to foods as a cause of urticaria, time did not permit Dr. Fink to go into this phase of the problem in detail, although the body of our paper analyzes this etiologic factor. We have found that eggs, milk, and wheat are the most common offenders. Drugs also have been given consideration, and I am rather surprised, although I am sure it is a known fact, that no mention is made in this discussion of the drug "atophan" as a cause of urticaria. It is a very definite factor in many instances when it is taken for arthritis. Those who develop urticaria following the administration of this drug may have the urticarial rash for as long as three months after the discontinuance of the atophan. It seems to be extremely toxic and acts more like a toxin than a foreign protein.

The parasites which we have encountered in our series of patients, have been scabies. After identification of the organism and after specific treatment for eradication the urticaria immediately subsides.

The Effect of Sinus Surgery in Asthma With Infection. R. CLARK GROVE AND R. A. COOKE, NEW YORK CITY. (Abstract.)

A group of 120 cases of asthma with infection were studied very carefully from the allergic and rhinologic aspects. Two hundred and forty-seven intranasal sinus and radical antrum operations were performed on these patients, who were subsequently followed for from six months

to three and a half years. A new approach to the proper evaluation of the effect of sinus surgery upon asthma with infection is offered. This consists in (1) determination of any associated skin sensitization and its effect on the asthma, (2) division of the patients into those who have had all necessary sinus surgery completed and those who have not. Our results were as follows: (1) in the completely operated infective group 82 per cent definitely improved; (2) in the incompletely operated infective group 38 per cent; (3) in the completely operated combined infective and skin-sensitive group 88 per cent definitely improved; and (4) in the incompletely operated combined group 40 per cent. The improvement in the total 120 cases was 70 per cent. We feel that if the cases are properly selected and completely operated, the results are decidedly encouraging.

DISCUSSION

Dr. Leslie N. Gay, Baltimore.—As Dr. Grove and Dr. Cooke have pointed out by a brief review of the literature, great confusion exists as to the relative advantage of removing chronic infection of the antrums, or, on the other hand, of permitting it to remain, provided adequate drainage is maintained in the asthmatic patient. I believe that there is a good reason for pessimism because of the countless failures which we encounter in asthmatic individuals who have had repeated surgical procedures in an effort to eliminate infection in the upper respiratory tract.

One must go further, however, and try to find the cause of the failure. It is safe to say that in many instances the infection is overlooked for months after the onset of the asthma, due to the inexperience of many physicians not trained in this special field or because of timidity on the part of the laryngologist to do a complete job when he first operates to remove the infected antral tissue, ethmoid and sphenoid cells.

Dr. Grove's teacher, Dr. S. J. Crowe, is a most conservative and scientific investigator, and my opinion is based on my contact with his work. Experience has taught us that the simple window will drain an antrum. It is not going to relieve the asthma, however, unless the infected columnar epithelium together with the mucous glands which infiltrate this lining membrane are completely removed. If islands of glands are left behind, regeneration will soon recover the wall, but if there are no islands from which these columnar cells and glands can spread, then a flat squamous epithelium will spread uniformly within the antrum. An infection cannot reestablish itself in this type of tissue.

The removal of this infected tissue is also important in patients suffering with acute nephritis. Dr. Longcope is particularly interested in this disease, and in his investigations in conjunction with Dr. Crowe it has been found that a pure culture of streptococci has been isolated in the nose. Even in the absence of any purulent discharge, x-ray studies have revealed a thickening of the antral mucous membrane. The tissue has been removed. It has been sectioned, stained, and has been found impregnated with streptococci. This tissue has also been macerated, and the same organism which has been found in the nose has been grown from the tissue so cultured. At the same time the secretory function, which has been dependent on the mucous glands, has been eliminated.

With regard to the use of iodine injections in x-ray studies of the sinuses, we rather oppose this method of diagnosis. We do not feel that the iodine injection of the sinuses is a necessary procedure. With careful technic it is not difficult to demonstrate soft tissue in the nose and also in the sinus cavities. The soft film is desired for this demonstration and not the clear-cut black film which we so frequently see and which, of course, entirely eliminates mucous membrane tissue, even though it outlines remarkably well the bony structures.

Even so, failure is encountered. Time is the handicap. In our experience the result of thorough surgery on the upper respiratory tract is disappointing unless the chronic bacterial group of asthmatic individuals is taken in hand before the respiratory distress has been of too long standing. This fact seems to hold, no matter how completely the infected membrane is removed. One can feel optimistic if the symptoms have been of one year's duration, but with every month thereafter prognosis must be guarded.

I am interested to know Dr. Cooke's opinion on this point and also to know, if the figures are available, the average duration of asthma in his reported group before the complete removal of the infection.

On the nose and throat service of Dr. Crowe, there is no halfway procedure in this group of patients. Either a thorough elimination is carried out when it is established that the disease of the antrums or sinuses is of a chronic type, or no surgery is resorted to.

I am in accord with this method of treatment, which Dr. Grove and Dr. Cooke have just discussed, as it seems to offer the greatest possible relief to individuals suffering with recurring attacks of asthmatic bronchitis.

DR. GROVE.—I am sorry that I could not go into details about the effect of the duration of the asthma on the results. That was in our original paper which had to be cut down. Dr. Kern and Dr. Schenk reported in their paper that the duration did not have much effect on the asthma. I used to think that the duration did amount to a whole lot, but unless patients have a marked chronic bronchitis, if they are completely operated and have not got into a too advanced or chronic stage, the duration of the asthma is not a factor. I should say the average duration of the asthma in our series would be four or five years for the whole 120.

One thing I would say in closing concerns the question of time in evaluating results. Do not be too optimistic in the first six months. Do not worry because the patient does not wake up free of asthma or other symptoms in the next week. The ratio of the unimproved to improved in the six months to one year group was one to one (fifty-fifty); but when you get to the one to two year group, the ratio of unimproved to improved was 1 to 2.6; and when you got to the two to three and a half year group, the ratio jumped to 1 to 3, so it is a question of time.

DR. HARKAVY.—What does the time do?

DR. GROVE.—I think it is elimination of infection, giving the patients a chance to get built up.

Migraine Headaches. Recent Advances in Classification, Diagnosis, and Treatment.* F. H. WESTCOTT, NEW YORK CITY. (Abstract.)

Forty cases of migraine were selected because they fulfilled the rigid requirements of such a diagnosis. They were analyzed particularly from a standpoint of hormonal balance, allergic influences, and general systemic function. They were classified as follows: predominantly allergic, 14 cases; predominantly toxic, 10 cases; predominantly endocrine, 9 cases; predominantly nervous, 5 cases; unclassified, 2 cases.

Of the 14 allergic patients, 10 had a family history of allergic diseases; and in 11, allergic manifestations occurred in their past history. All of these patients had marked dermal reactions to one or more allergens. The average number of positive tests was 10. The most frequent were to wheat, egg, tomato, orange, potato, beef, veal, and peas. A diet omitting all of these foods, in addition to any others which seemed to be of causal importance, was instituted. Thereafter a food diary was kept, and foods were added one at a time in the usual manner. When indicated, inoculations with pollens, dust, epidermal extracts, and vaccines were given.

It was pointed out that the skin tests could be fallible. The number of positive dermal tests to foods found in migraine was 15 per cent, as compared with 12.4 per cent in nonallergic patients, and 16.3 per cent in allergic diseases other than migraine. Twenty-two of the 40 cases, or 55 per cent, presented no evidence of allergic disease. These findings are not in keeping with those of other investigators.

Of cases classified as endocrinopathies, there was a family history of allergy in 40 per cent, and of endocrine dysfunction in 20 per cent. Basal metabolic readings were usually below normal, and dysfunction of various endocrine glands was frequently in evidence. Glandular therapy such as thyroid, glycerine extract of adrenal tissue, and theelin, was used. Experiments with adrenalin or ephedrine have not justified their routine use.

The cases considered to be toxic were those that showed very few signs of either of the aforementioned causes. In most instances, foci of infection, bowel disorders, or nonallergic indigestion with chronic digestive upsets, were found. Frequently useless surgical procedures in this group of patients had been performed. The frequency of precipitating causes of attacks were special foods (16), digestive upsets (16), nervous strain (15), physical strain (15), menstrual cycle (14), and multiple factors (33).

From this analysis it appears that: (1) Migraine is a symptom complex entity in itself and should not be considered as just a symptom of some other disease. (2) There are three main constituents to a

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migraine make-up—heredity, predisposing factors, and exciting factors. (3) There is no single constant exciting factor to explain all migraine. (4) Allergic migraine is estimated to comprise about 35 per cent of migraine cases and when properly classified will respond favorably to the indicated therapeutic measures.

DISCUSSION

Dr. J. H. Barnard, New York City.—It seems worth while first to stress one of Dr. Westcott's early statements, namely, that these cases were especially selected from a much larger group because they conformed in the strictest sense to the syndrome known as migraine.

As far as I have been able to observe from skin tests and clinical observations, his percentage of cases most probably allergic in origin is nearer right than the very high percentages we have read of in the past. On the other hand, with further chemical advances whereby sensitivity to split products of digestion and autolysis may be demonstrated, cases now thought to fall in other groups may prove to be allergic. However, for the present the fallacy of too liberal interpretation of moderately positive skin tests, particularly to foods, must be kept in mind.

From histories and observations of cases of migraine we have been led to believe that fish, chocolate, milk, and spices are often offenders, and all the more probable because of their frequency in our present-day diet.

It may well be that the modification of the test diet will be a step forward. Certainly it has the factors of time saving and greater comfort to the patient in its favor.

A patient I have in mind would have to be included in all groups: for the allergic side, with a positive family history for allergy, she frequently has severe vasomotor rhinitis, hives, and slight wheezing with attacks of migraine; against this, all skin tests were negative and diets have availed nothing. For the endocrine side, she is worse during menses, but was better when pregnant. Thyroid, ovarian, and other endocrine medications were of no help. For the toxic side, she has a history of marked constipation for years. A neurogenic basis has been suggested for her trouble, yet neurologists are turning to the above factors for their etiology. I can well understand how a recurrence of this distressing condition time after time over long enough periods would bring any one under the label of a neurotic.

Dr. Westcott has drawn attention to the gastrointestinal features of the toxic cases in particular. I wonder whether the same system is not usually affected to more or less the same extent, whatever the etiology. His reference to the frequency of gallbladder removals in treatment, brings to my mind the fact that a member of a well-known gastrointestinal clinic told me about three years ago that a large, flabby, poorly emptying gallbladder was frequently found in their migraine cases. Recently he told me that they now believe that most of their cases have the origin of their trouble in a dilated, poorly emptying duodenum, and patients have been subjected to surgical procedure in an attempt to relieve it. The treatment outlined in the paper seems much more preferable.

As Dr. Westcott pointed out, it is possible that allergic factors may

be dependent on the variable condition of the patient at different times, i.e., state of exhaustion, digestion, and so forth.

DR. HORACE S. BALDWIN, New York City.—In migraine the foregoing analysis of the various excitants is fundamental to any therapeutic handling of this condition. It seems clear that allergic excitants may play an important rôle in certain cases, but that it is only from a complete study of all the excitants in the individual case that the best results can be obtained. Unfortunately, we are handicapped by lack of knowledge concerning the pathology of migraine and to a considerable extent by certain gaps in our knowledge concerning the pathologic physiology of brain and meningeal circulation. Until our knowledge of these very fundamental facts is greater than it is today, our therapeutic rationale will necessarily lack conviction and finality.

DR. WARREN T. VAUGHAN.—The question has been raised whether we should speak of "allergic migraine" or of "allergic headache." Acting under the stimulus of that question, I have completed what to me is a very thorough survey of my entire migraine series. On the basis of this survey, I can state with most positive assurance that the longer you talk with your migraine patient and the more carefully you study his history for minor allergic manifestations, the higher percentage of allergic manifestations you will find. My figure is 70 per cent.

At the same time, I will say that of those who claim 82.5 per cent cure from allergic therapy, the only basis therefor is hyperenthusiasm. My own experience is about 50 per cent.

I have a few figures here I want to give you. When we speak of allergic migraine, we are talking about *migraine*—in my series they are true cases of migraine and fulfill every requisite. You cannot predetermine from the symptomatology whether you are going to get good results or not. But they are all migraine.

There are two points that came out in the survey: (1) where the migraine is associated with the catamenia, you do not get as good results; (2) where it is predominantly bilateral, you do not get as good results; otherwise you cannot get anything from the symptomatology to indicate what results you will get.

In a survey of 508 individuals in a homogeneous population, 7 per cent had recurrent paroxysmal headaches, and every one of them could tell what food caused them. Seven per cent already knew, without ever going to the physician, that they had headaches due to specific foods and could name the foods. We have had no idea how common it is, and how often the patient himself has diagnosed the cause of his headaches.

In an allergic series of 85 individuals, consecutive patients who came in this winter, we made a survey of those headaches that the patient himself knew were due to foods. None of them came in for migraine; all of them came in for other allergic manifestations. But as contrasted with a general population that has 7 per cent recurrent paroxysmal headaches, the allergic individuals have upward of 30 per cent headaches due to specified foods.

Effects of Immunization Upon Vaccine Skin Reactions. M. D. TOUART, NEW YORK CITY. (Abstract.)

Immediate (early) and delayed (late) skin reactions following intracutaneous vaccine injections were described and defined. An analysis of data from the case histories of 33 patients tested and treated with autogenous vaccines, for various types of bacterial allergy, was presented in the form of tables and charts. These data appeared to indicate:

1. That regardless of the degree of success of vaccine treatment, the relation of the early or wheal reaction to the injection of vaccines remained substantially unchanged.

2. That regression of the late vaccine skin reaction, on the other hand, occurred in the majority of successfully treated patients but failed to occur in most of the patients who received no benefit from vaccine treatment. Such regression also failed to occur in the skin reactions produced by vaccines not used in treatment.

3. That the degree of regression or diminution in intensity of the late vaccine skin reaction was in direct proportion to the degree of improvement in the patient's symptoms.

The following conclusions seemed to be warranted:

1. That the late type of vaccine skin reaction, in addition to being a useful guide in the selection of vaccines to be used in treatment, is also an indicator of the progress of desensitization to bacteria in vaccine treated patients.

2. That decrease in intensity of the late skin reaction to vaccine, occurring synchronously with decrease in the symptoms of a patient during properly conducted vaccine treatment, appears to point to a parallelism between those symptoms and a specific sensitization to the organisms contained in the vaccine.

DISCUSSION

DR. WARREN T. VAUGHAN.—I think we are all very much in the same condition so far as bacterial allergy is concerned. We want to know more about it, and we hope the other fellow will undertake a lot of work on the subject. I know we are all glad that Dr. Touart, Dr. Thomas, Dr. Famulener, Dr. Brown, and some of the others, are working on it.

It is hard to see just where these observations are getting us, but they are bound to lead somewhere. I could not help wondering what possible connection there was between these observations and those recent ones by Rich on the disappearance of the tuberculin type of reaction. He has found that experimentally tuberculin desensitization does not diminish tubercle bacillus immunity in animals. This would suggest that desensitization therapy does not decrease immunity to infection. I wonder whether Dr. Touart has any suggestions to make on this.

I think the observations of Dr. Rich are especially interesting because we are injecting so much material into people who often ask, "Won't it make me more susceptible to colds or other infections?"

A Case of Epilepsy Presenting Unusual Manifestations. H. B. WILMER AND M. M. MILLER, PHILADELPHIA, PA. (Abstract.)

A case of a man, aged thirty-two years, was reported. His present illness began at the age of nineteen years. While riding a street car he was suddenly taken ill with nausea, severe headache, dizziness, and mental confusion. From this attack he gradually spontaneously recovered. The attack was followed by some difficulty in vision and intense head pain. Soon after, he became jaundiced, during which time he was very sleepy and not mentally alert. After this he was sent to a hospital for observation, and was there for two months. One week after admission he had a convulsive seizure while asleep, at which time he bit his tongue. The convulsion was generalized. For a day thereafter he was very nervous and irritable.

On reentering college, he had difficulty in thinking clearly, and seven months later he had another convulsion while asleep, similar to the first. On a starvation diet for eleven days, he remained free from trouble. After that he complained of sleepiness, and it was often necessary for him to drink large amounts of coffee to keep awake.

Three months later, a third convulsion occurred, again while asleep. Despite a starvation diet this attack was followed by nervousness, mental depression, and reduction of sexual power. Epileptic seizures, headaches, and depression occurred during the next three months. A diagnosis of psychoneurosis was made in a psychiatric clinic at that time. Finally the epileptic attacks ceased, but there were almost continuous headaches and general malaise.

A year later epilepsy again appeared, and an exploratory operation of his skull was made but nothing was found. For the next five years there was an increasing sensitivity of the left hand manifested by pain in his arm if the hand were irritated, and this pain if severe would be followed by convulsive seizures.

It was suggested then that he take Epsom salts every day for a period of time. This brought relief until his intestinal tract became very irritable. Then the left-sided attacks reappeared, and they finally occurred as often as a dozen times a day. Encephalograms then showed no findings.

He was put through an allergic study, and showed a 2 plus reaction to corn pollen and crab, and 1 plus to other pollens and foods. By the intradermal method he gave a 3 plus reaction to apple, pear, black pepper and duck feathers, 2 plus to house dust, coffee, onion, garlic, and asparagus, and 1 plus to a variety of foods. He was placed on a diet eliminating all foods to which he reacted, but with no results.

Rowe's elimination diets were next tried. Diet 1 was followed by marked improvement, and he was free from symptoms for three months. On Diet 2 he had one slight attack, but he took most of his food from

Diet 1. To this combination, milk, tomato juice, and cod liver oil were added. Since that time the patient felt very well, was not fatigued more than normally, nervously he was greatly improved, and he had no mental depression. He still has a mild hypersensitivity to external stimuli in his left arm and hand, but he has not had any marked convulsive seizures since he started on the diet, nor has he lost consciousness since then.

The authors believe that this patient is possibly a case of allergic epilepsy.

Department of Reviews and Abstracts

Selected Abstracts

Passage of Native Proteins Through the Normal Gastrointestinal Wall. Ratner, Bret, and Gruehl, H. L.: J. Clin. Investigation **13**: 517, 1934.

The authors point out that the view most generally held today is that undigested antigens are not absorbed through the normal gastrointestinal wall, and that when such absorption does occur it is because abnormal or pathologic conditions exist, such as stasis, the excessive flooding of the intestines with protein foods, lessened activity of the intestinal enzymes, altered conditions of the intestinal mucosa, and greater permeability of the intestinal wall characteristic of newborns and sucklings.

There is some contention about this point, and the authors set out to study the question by direct experiments. They found that mature as well as young animals can be sensitized and shocked by the oral administration of protein foods. The incidence of positive results in a large series of animals was as high as 50 per cent. Experiments were carried out within physiologic limits. This is offered as conclusive evidence of the fact that unsplit proteins pass the intact intestinal wall under normal conditions.

In the human being it was shown that proteins natural as well as foreign to the diet pass the intestinal wall and may enter the blood stream under physiologic conditions at all ages. Although normal and pathologic conditions of the intestinal mucosa increase intestinal permeability and facilitate the passage of unchanged proteins, the authors believe that under normal conditions absorption of unaltered protein occurs with great regularity. It is suggested that this normal absorption may conceivably serve the useful purpose of constantly maintaining the body in a state of immunization against habitual protein diets.

CO_2 Inhalation in the Treatment of Bronchial Asthma. Faragó, P.: Ztschr. f.d. ges. exper. Med. **91**: 114, 1933.

This treatment is based upon the conception that during an attack of bronchial asthma there is a disturbance of the acid-base balance toward the alkaline side. Some confirmation of this theory is found

in the literature, wherein ketogenic diets and acid therapy have proved beneficial during asthmatic attacks.

Twenty-three patients with bronchial asthma were given injections of 8 per cent CO_2-O_2 mixture through a Drager apparatus. Twelve liters of the mixture per minute were administered, and the treatment was given at increasing intervals lasting from fifteen to twenty minutes. Chemical analyses on the blood and urine were made at intervals after the treatment. Distinct benefit was noted in a fair portion of the patients so treated.

Following the inhalation there was a diminution of the alkaline reserve and the blood lactic acid rose. The pH of the urine remained unchanged.

The Mechanism of the Urticarial Idiosyncrasy to Egg White in the Eczematous Child. Jadassohn, W., and Schaaf, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**: 407, 1933.

Dialysates of egg white are known to be urticariogenic in certain eczematous children with allergy. Opinions differ as to whether the reacting substance is of protein nature, or a nonprotein substance. When the proper technic is employed, no protein substances pass into the dialysate. The comparison, by means of the Prausnitz-Küstner technic, of the urticariogenic potency of egg white and of dialysate revealed that the latter reacted in quantities which could not contain the minimum concentration of protein found necessary in quantitative tests with egg white. By means of the Prausnitz-Küstner technic it was also possible to demonstrate that chicken egg white contains at least two antigenic substances; one of them is also present in duck egg white. Both pass through the dialyzing membrane. The blood serum of eczematous children with urticarial hypersensitiveness to egg white contains substances which can neutralize the urticariogenic properties of egg white.

Cottonseed Allergy. Taub, S. J.: J. A. M. A. **103**: 334, 1934.

Of 246 allergic patients, each of whom was tested with some 300 separate allergens, 13 reacted specifically to cottonseed. This gives a percentage of 5.3 per cent positive reactions, as against about 2 per cent reported by other observers. The tests were done by the scratch method.

The point is made that patients sensitive to cottonseed usually manifest an eosinophilia somewhat higher than the average allergic individual.

The various sorts of cottonseed as an ingestant are given as follows: lard substitutes, butter substitutes, sardine packing, olive setting,

bakery goods including their use as a coating to hold chocolate firm, Wesson oil, Crisco, cottolene, and cottonseed oil. As a contactant, it is used in cosmetics, in the compounding of emulsions by druggists, as a base for liniments. It is also used in salves and camphorated oil. As an inhalant it is found in mattresses, pillows, blankets, and stuffing in furniture. It is also used on greens and fairways, and as cattle food.

Treatment of Hay Fever and Its Allied Conditions by Ionization. Preliminary Report. Warwick, H. L.: Laryngoscope **44**: 173, 1934.

More than ten years ago Demetriades demonstrated a method for the treatment of hyperesthetic rhinitis which he termed "Iontophoresis," wherein the nose was packed with cotton wool saturated with an electrolyte containing calcium salts. In the midst of the packing was inserted a zinc electrode which in turn was connected to the positive pole of a galvanic apparatus. Using from two to three milliamperes of current over a period of from five to ten minutes, he was able to obtain considerable relief in the patients' symptoms. He believed that the positively charged metallic ions which were driven into the nasal mucosa desensitized the nerve endings and made them less susceptible to irritation by allergens.

This method has had several modifications, including that of the author. He packs each side of the nose with 10 per cent cocaine in 1.5 per cent ephedrine solution for ten minutes. The ionizing solution used is a combination of zinc, cadmium and tin, with their respective salts. A special resistance meter is connected with the patient. The author found 2,500 to 3,000 ohms resistance to be quite satisfactory. Various other refinements of the original method are described.

A series of 40 cases in which the patients have been entirely relieved of their symptoms for more than a year is reported. Hay fever was the major allergic complaint. Four had asthma in addition, and six had perennial hyperesthetic rhinitis. All but one of these patients had been entirely relieved of their symptoms for more than a year, and 19 of them for more than three years. Thirty-one required only one ionization for complete relief, seven required two ionizations, and one three ionizations before permanent relief was obtained. One patient was entirely relieved for one year, and returned and was given two more ionizations without any relief whatever. A table with results in individual cases is given.

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